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METABOLISM STUDIES IN NEPHROSIS

WITH SPECIAL REFERENCE TO THE RELATIONSHIP OF PROTEIN INTAKE TO NITROGEN RETENTION, EDEMA AND ALBUMINURIA *

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To attract attention to that group of metabolic disturbances that manifests itself by the development of edema without the cardiovascular mechanism necessarily being involved, we are using the term nephrosis. These disturbances are commonly believed to be of renal origin or to be associated with kidney dysfunction of some kind. The fact is well established that cardiovascular disturbances and kidney disease may lead to generalized edema, and the explanation for the occurrence of edema under these circumstances seems quite clear. It is not clear how generalized edema may occur in the absence of primary disease in these systems. It is conceivable that some underlying fault of metabolism may bring about characteristic changes in the kidneys which are not necessarily confined to these organs but which may, on careful search, be shown to involve other structures of the body in a similar way.

We present a study of a case of so-called nephrosis which differs from the well described type chiefly in the consistent finding of a relatively high basal metabolic rate. Determinations of the nitrogen balance were carried on uninterruptedly for a period of 105 days.

REPORT OF CASE

History.—Leo O., aged 6 years, entered the clinic on April 12, 1928, because of generalized anasarca. He had had measles (?) when 3 weeks old, the rash lasting only one day. For two years preceding 1927, he had had frequent attacks of fever

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* Presented at the meeting of the American Pediatric Society, St. Louis, May, 1929.

* From the Department of Pediatrics and Infectious Diseases, University Hospital.

and vomiting, which never lasted for more than two days. The temperature was as high as 104 F. During this period, one severe hemorrhage from the nose is recorded. The present illness began one year before admission with "swelling" of the abdomen and scrotum. Large amounts of albumin are said to have been present in the urine. The swelling gradually increased, involving the lower extremities, face and chest, but not the upper extremities. The abdomen became so large that tapping was necessary, and large amounts of fluid were removed on several occasions. The patient had never been free from edema until after he entered the clinic. His appetite had always been good. There had been no digestive disturbances and no headaches.

At the birth of the child instrumental delivery had been necessary. He weighed 8 pounds (3.6 Kg.). He was breast fed for eight months; then, in sequence, were given condensed milk, dextrimaltose and milk and oatmeal until he took ordinary food. The first tooth appeared at 5 months of age. He sat up alone at 11 months, talked at 12 months and walked at 22 months.

Examination.—On April 12, 1928, the patient weighed 57 pounds (25.7 Kg.), and was 101 cm. in height; he appeared to be poorly nourished, chronically ill and very pale, with puffiness of the face, marked fluid distention of the abdomen, umbilical hernia, marked edema of the lower extremities and no edema of the upper extremities. Complete neurologic examination gave negative results. He walked very slowly, and was very inactive in all his movements.

There was an area of dulness over the bases of both lungs to the angle of the scapula. A few fine râles were heard over these areas; otherwise, examination of the lungs gave negative results. A roentgenogram showed a high diaphragm on both sides.

The left border of the heart was felt inside the nipple line. There were no murmurs and no arrhythmia or thrills. The sounds were of good quality. There was normal heart shock. The blood pressure was 90 systolic and 70 diastolic. A roentgenogram showed the heart to be slightly displaced upward.

The abdomen was balloon-shaped and distended 7 or 8 inches above the level of the chest. The superficial veins were plainly seen, and a fluid wave was noted. An umbilical hernia, 5 cm. in diameter, protruded 2 cm. above the abdominal wall. The skin was tense. After paracentesis, the liver and spleen were palpable.

Genito-urinary examination gave negative results. There was no edema.

Urinalysis showed: specific gravity, 1.025,[1] acidity; albumin, 4 plus; many casts, red cells and cylindroids. There was no excess of leukocytes, and no sugar. The water intake was approximately 1,000 cc.; the output, 120 cc.

Examination of the blood revealed: red cells, 3,290,000; white cells, 14,540; hemoglobin, 66 per cent; polymorphonuclears, 72 per cent. Nonprotein nitrogen, 23 mg. per hundred cubic centimeters; serum protein, 4.1 per cent; serum albumin, 2 per cent; serum globulin, 2.1 per cent; ratio, 0.95; cholesterol, 523 mg. per hundred cubic centimeters; blood chlorides, 511 mg.; inorganic phosphate, 4.9 mg.; serum calcium, 8.2 mg., and carbon dioxide combining power, 44.7 per cent by volume.

Seven thousand cubic centimeters of ascitic fluid was removed. Examination showed it to be chyliform, with traces of fat and cholesterol; protein, 0.3 per cent; chlorides, 643 mg.; nonprotein nitrogen, 14.2 mg.; sugar, 0.104 per cent.

The Wassermann reaction of the blood was negative. The Mantoux test was negative. The basal metabolic rate was + 20 and + 19.

1. This is not a true index of this patient's ability to concentrate his urine. It was subsequently shown that after deducting the influence of the albumin content on the specific gravity his concentrating ability was within normal limits.

Otologic examination showed chronic septic adenoids and tonsils and normal sinuses.

Dental examination showed eleven carious and abscessed teeth. The upper and lower deciduous molars and the lower permanent first molar were removed.

The fundi were normal on repeated examinations.

The intelligence quotient was 109.

First Admission.—April 12, 1928, to Aug. 25, 1928 (table 1): The patient was kept on an adequate protein diet for the greater part of his stay in the hospital. Toward the end of this period the edema and ascites became so reduced that he

TABLE 1.—*Preliminary Data*

	April 14, 1928	May 7, 1928	July 3, 1928	July 18, 1928	July 24, 1928
Urine					
Urine, cc.	120	....	1,000	920	600
Specific gravity	1.025	1.011	1.013	0.013	1.006
Albumin	++++	0.8%	++	0.6%	0.62%
White cells	....	+	±	±	0
Red cells	+++	+	0	±	0
Casts	+++	+	±	+++	+
Blood Chemistry					
Nonprotein nitrogen, mg.	23.0	21.0	22.6	25.6	27.0
Serum protein, per cent	4.1	5.4	5.0	4.7	4.8
Serum albumin, per cent	2.0	....	1.1	1.4	1.5
Serum globulin, per cent	2.1	....	3.9	3.3	3.3
Albumin-globulin ratio	0.95	....	0.30	0.42	0.45
Chlorides, mg.	511	606	519	511	470
Calcium, mg.	8.2	....	....	....	....
Phosphorus, mg.	4.9	....	....	....	....
Carbon dioxide combining power, per cent by volume	44	....	....	....	....
Sugar, per cent	0.108	0.105	....	0.94	0.104
Cholesterol, per cent	0.523	0.580	0.530	0.525	0.550
Creatinine, mg.	....	....	....	1.7	1.6
Ascitic Fluid					
Nonprotein nitrogen, mg.	....	14.2	....	....	....
Serum protein, per cent	....	0.3	....	....	....
Serum albumin, per cent	....	0.0	....	....	....
Chlorides, mg.	....	643	....	....	....
Cholesterol, per cent	....	Trace	....	....	....
Fat	....	Trace	....	....	....
Sugar, per cent	....	0.104	....	....	....
Miscellaneous					
Red count	3,200,000	3,610,000	....	4,480,000	....
White count	14,540	7,000	....	15,150	....
Hemoglobin (Sahli) per cent	66	60	....	60	....
Blood pressure	....	90/70	92/60	104/78	92/61
Basal metabolism	....	....	+20*	+10†	....
Diet	House diet	High protein	High calorie	Protein 27 Gm. daily	Protein 27 Gm. daily
Weight, Kg.	25.7	18.7	17.7	17.6	17.7
Edema	++++	+	0	0	0

* June 29.
† July 11.

was able to be up and about and carry on normal activities. Observations on nitrogen balance were begun on August 25, just prior to his discharge. We were obliged to discontinue them temporarily. The child was sent home, and was placed on a diet consisting of 27 Gm. of protein, 87 Gm. of carbohydrate and 97 Gm. of fat. The daily output of urine, which was low on admission, had increased to as high as 1,000 cc. The albumin was reduced to 0.62 per cent. The red blood cells had disappeared, and only an occasional cast was found. The nonprotein nitrogen of the blood was constantly normal. The serum protein varied from 4.1 to 5.4 per cent. The albumin-globulin ratio continued to be reversed (0.45). The cholesterol values were practically the same throughout. The red blood count had increased to 4,480,000. A leukocytosis continued (15,150).[1]

1. Due to abscessed teeth and septic tonsils.

Because of the hematuria, casts and the prolonged course of the disease, chronic glomerular nephritis was considered as a working diagnosis. The normal blood pressure, the high cholesterolemia, the low serum protein and the reversed albumin-globulin ration inclined us to the belief that the condition was progressively advancing into the nephrotic subgroup of glomerular nephritis.

Second Admission.—Sept. 27, 1928, to Feb. 6, 1929: The patient kept well to his diet during a month's stay at home, ingesting approximately 27 Gm. of protein daily. There was no recurrence of edema. The child was able to follow his normal activities. There was no appreciable change in physical observations. At this time he weighed 37 pounds (16.8 Kg.). The tonsils showed infection; the cervical glands were palpable, and the abdominal walls were flaccid.

From September 27 to October 25, specimens of urine and stool were used for checking and developing a good technic preparatory to studies on the nitrogen balance. These studies were begun on Oct. 25, 1928, and continued to Feb. 6, 1929, 105 days. The time was divided into four periods, according to the protein content of the food (table 2).

First period,[3] twenty days, October 25 to November 13: A daily average of 45.4 Gm. of protein was ingested (1.2 Gm. per pound, 2.6 Gm. per kilogram). Second period, twenty-five days, November 14 to December 8: A daily average of 25.4 Gm. of protein was ingested (0.68 Gm. per pound, 1.5 per kilogram). Third period, twenty-five days, December 9 to January 2: An average of 17.9 Gm. of protein was given daily (0.47 Gm. per pound, 1 Gm. per kilogram). Fourth period, thirty-five days, Jan. 3 to Feb. 6, 1929: An average of 66.7 Gm. of protein was given daily (1.7 Gm. per pound, 3.8 per kilogram).[4]

Procedure.—The preparation of the patient's diet was carefully supervised by our departmental dietitian, Miss Frances Floore. The protein, fat and carbohydrate of the food were estimated from the Atwater tables. Food that the child refused was carefully weighed and discounted from the individual meal offered. The daily fluid content of the diet was measured by the nurse in charge of the case, but since several nurses were employed during the course of the experiment, we preferred to regard the estimations on the fluid intake as being subject to a probable source of error. A twenty-four hour specimen of urine containing 1 cc. of concentrated nitrogen-free hydrochloric acid was collected daily. The specimens were measured and analyzed by the same person. Stool specimens were collected in special containers containing thymol. In estimating the nitrogen in the stools, determinations were made from total five day specimens and a daily average calculated. The stools were mixed thoroughly and dried to constant weight before analyses. We believe that this procedure is more satisfactory than estimations on twenty-four hour specimens. The daily quantity of urinary albumin was estimated by the Esbach method, Tsuchiya's reagent being used. A determination of the child's basal metabolic rate was made for each experimental period, and these determinations can be considered reliable because of the excellent cooperation obtained from the patient. All blood specimens were obtained before breakfast.

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3. During the first period there was three times as much base as acid in the diet, the second period three times, the third period seven times, the fourth period two times. There was a deficiency of calcium and phosphorus in the diet of the second and third periods, and a sufficient amount in the first and last periods of adequate protein feeding.

4. Average weight during edema-free periods at beginning and end of experiment, 38.5 pounds (17.5 Kg.).

Chemical Methods.—Nitrogen in the urine and feces was calculated by the Kjeldahl method; the nonprotein nitrogen by the method of Folin and Wu, and the serum proteins by the micro-Kjeldahl method. Globulin was precipitated by sodium sulphate (22.2 per cent). Chlorides were estimated by the method of Whitehorn ($AgNO_3$ titration with ammonium sulphocyanate); cholesterol by the modification of Bloor's method by Sacket; calcium by the Clark and Collip modification of Kramer and Tisdall's method; phosphorus by the method of Fiske and Subbarow. (Special care was taken to avoid an excess of oxalate in collecting the blood specimens for phosphorus determinations. Excess of oxalate inhibits the development of color in this method, a low reading being thereby obtained.) Creatinine was estimated by the method of Folin.

COMMENT

Edema.—As evidenced by increase in weight (chart), edema began to develop in the middle of the second period. It became most marked during the early part of the fourth period just following the period of lowest protein intake (17.9 Gm. a day). During this period of edema, there was a gain of 8.8 pounds (4 Kg.).

Disappearance of Edema.—On January 3, the protein content of the diet was gradually raised to 70 Gm. a day. This point was reached on the fifth day of the fourth period. Four days later, the weight had decreased 9 pounds (4.1 Kg.) and the clinical evidence of edema had disappeared. This marked loss of weight was associated with a phenomenal output of urine as compared with the output of previous periods. At the end of the third period the urine output had been as low as 280 cc. a day. It now rose to 2,670 cc. on the sixth day of the last or highest protein period. The patient was kept on this protein intake for the remaining twenty-seven days of his stay in the hospital. During this time his physical condition was practically normal. His weight was 38.25 pounds (17.4 Kg.). However, the urine continued to contain as much as 6.2 Gm. of albumin per liter per day (chart).

Effect of Protein Intake on Albuminuria.—During the first period of adequate protein feeding, the albumin output varied from 0.7 to 5.9 Gm. per day (average 3.6 Gm.). During the second or inadequate protein period, the daily albumin ranged from 2.1 to 9.6 Gm. per day (average 4.9 Gm.). During the third or still more inadequate protein feeding period, the albumin output varied from 1.8 to 9.3 Gm. (average 4.2 Gm.), practically the same as it was during the adequate protein period. For the first twelve days of the highest protein period, the albumin output was greatly increased. It varied from 5.7 to 18.8 Gm. per day (average 10.1 Gm.), an increase of practically 150 per cent. After these twelve days the albumin output rather quickly adjusted itself to a lower level, ranging from 1 to 11 Gm. per day (average 6.6 Gm.) (table 2, period IV). The average albumin output for this last adequate protein feeding period (period IV) was 8.3 Gm. per day.

TABLE 2.—*Studies in Nitrogen Balance*

Date	Nitrogen Balance: Intake, Gm.	Output in Gm.: Urine	Stool	Total	Balance, Gm.	Weight, kg.	Food: Protein, Gm.	Fat, Gm.	Carbohydrates, Gm.	Calories	Urine: Cc.	Albumin, Gm. per Liter	Albumin, Daily Total, Gm.	Sediment	Comment
Period I—Adequate Protein Feeding															
10/25/28	6.40	3.90	0.55	4.45	−2.15	.....	49	68	113	1,280	850	3.7	3.8	Crystals	
10/26/28	7.52	5.12	0.35	5.47	−2.05	.....	47	59	131	1,279	700	4.1	2.8	Crystals	
10/27/28	7.84	5.17	0.35	5.52	−2.32	17.58	49	65	124	1,214	990	6.9	7.9	Crystals	
10/28/28	7.84	4.10	0.35	4.45	−3.39	.....	49	70	102	1,104	640	5.9	3.8	Crystals	
10/29/28	7.84	5.84	0.35	6.19	−1.65	.....	49	75	128	1,328	980	4.9	4.8	Crystals	
10/30/28	7.68	5.60	0.89	6.49	−1.19	.....	48	81	145	1,546	980	5.0	4.9	Crystals	
10/31/28	7.20	5.10	0.89	5.99	−1.21	.....	45	86	124	1,402	860	4.9	4.2	Crystals	
11/1/28	5.52	5.50	0.89	6.39	+1.13	.....	47	77	137	1,471	895	4.5	4.0	Crystals	Stool specimen lost
11/2/28	7.20	4.91	0.89	5.80	−1.40	.....	45	85	157	1,707	620	5.9	3.7	.....	Stool specimen lost
11/3/28	6.72	4.09	0.89	4.98	−1.74	.....	42	81	133	1,471	570	6.9	3.9	.....	
11/4/28	6.56	4.71	0.41	5.12	−1.44	17.01	41	88	109	1,433	690	1.0	0.7		
11/5/28	5.92	3.96	0.41	4.37	+1.55	.....	37	60	92	1,087	929	3.5	3.3	Crystals	
11/6/28	6.08	4.62	0.41	5.03	+1.05	.....	38	68	109	1,237	870	3.5	3.0	Crystals	
11/7/28	7.68	2.71	0.41	3.12	+4.56	.....	48	81	107	1,280	470	6.5	3.0	Crystals	
11/8/28	7.20	7.49	0.41	7.90	−0.70	.....	45	76	102	1,234	1,200	3.5	4.2	Crystals	Stool specimen lost; urine incomplete
11/9/28	6.24	4.78	0.68	5.46	−0.78	.....	39	70	138	1,311	720	4.5	3.2		
11/10/28	7.04	5.26	0.68	5.94	−1.10	.....	44	75	120	1,270	865	5.0	4.3		
11/11/28	8.00	2.50	0.68	4.78	+3.82	16.78	50	78	145	1,525	515	5.5	2.8		
11/12/28	8.80	6.36	0.68	7.04	+1.76	.....	55	70	131	1,434	822	3.5	4.6		
11/13/28	8.16	5.36	0.68	6.24	+1.92	.....	51	84	138	1,536	865	5.0	4.3	.....	R. R. L., −225
Average	7.28	4.81	0.76	5.39	+1.87	17.12	45.4	74.9	126	1,389	795	4.5	3.6		
Period II—Low Protein Feeding															
11/14/28	4.24	4.73	0.67	5.40	−1.26	.....	25.9	56.0	100.0	1,065	805	4.9	3.6		
11/15/28	4.24	3.73	0.67	4.40	−0.26	.....	25.9	56.0	100.0	1,065	760	4.5	3.3		
11/16/28	4.24	3.41	0.67	4.08	+0.06	17.69	25.9	56.0	100.0	1,065	670	5.5	3.6		
11/17/28	4.24	3.32	0.67	3.99	+0.15	17.69	25.9	56.0	100.0	1,065	760	6.0	4.6		
11/18/28	4.24	3.96	0.67	4.73	+0.41	17.69	25.9	56.0	100.0	1,065	655	10.0	6.5		
11/19/28	4.24	2.96	0.72	3.68	+0.46	17.80	25.9	56.0	100.0	1,065	685	9.0	6.3		
11/20/28	4.24	2.93	0.72	3.65	+0.49	17.80	25.9	56.0	100.0	1,065	720	7.0	5.0		
11/21/28	4.24	3.07	0.72	3.79	+0.35	17.56	25.9	56.0	100.0	1,065	550	9.0	4.9		
11/22/28	4.24	3.03	0.72	3.75	+0.39	17.46	25.9	56.0	100.0	1,065	655	6.5	4.2	.....	R. R. L., −217
11/23/28	4.24	2.93	0.72	3.65	+0.47	.....	25.9	56.0	100.0	1,065	850	3.5	2.9		
11/24/28	4.24	3.78	0.80	4.58	−0.04	18.14	25.9	56.0	100.0	1,065	590	6.0	3.5		
11/25/28	4.24	3.24	0.80	4.04	+0.10	18.14	27.7	60.9	118.3	1,204	665	6.0	4.0		
11/26/28	4.40	3.78	0.80	4.58	−0.07	18.14	25.7	59.0	147.0	1,297	765	6.0	4.6		
11/27/28	4.24	3.72	0.80	4.52	−0.04	18.27	25.7	59.0	147.0	1,297	765	5.0	3.8		
11/28/28	4.24	4.50	0.80	5.30	−1.19										

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

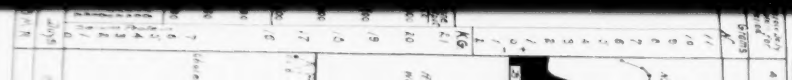
TABLE 2.—*Studies in Nitrogen Balance—Continued*

Date	Nitrogen Balance: Intake, Gm.	Output in Gm.: Urine	Stool	Total	Balance, Gm.	Weight, Kg.	Food: Protein, Gm.	Fat, Gm.	Carbohydrates, Gm.	Calories	Urine: Cc.	Albumin, Gm. per Liter	Albumin, Daily Total, Gm.	Sediment	Comment
Period IV—Comparatively High Protein Feeding—Continued															
1/16/29	11.28	9.78	0.56	9.74	+1.54	17.27	70.5	70.4	138.9	1,495	1,415	4.0	5.7	No casts	
1/17/29	10.68	9.09	0.56	9.65	+0.95	17.16	66.9	70.3	110.3	1,380	1,290	6.5	8.4		
1/18/29	11.28	8.94	0.57	9.01	+2.27	17.27	70.5	69.4	138.9	1,504	1,125	6.0	6.8		
1/19/29	11.28	8.61	0.57	9.18	+2.10	17.36	70.5	69.4	138.9	1,504	1,250	8.0	10.0		
1/20/29	11.28	8.90	0.57	9.47	+1.81	17.58	70.5	69.4	138.9	1,504	1,190	5.5	6.5	No casts	
1/21/29	11.28	7.82	0.57	8.39	+2.89	17.36	70.5	69.4	138.9	1,504	960	1.0	1.0		
1/22/29	10.34	10.98	0.57	11.55	−1.41	17.58	63.4	69.6	132.8	1,452	1,295	1.8	2.3	.....	B. M. R., +13%
1/23/29	10.78	8.57	0.69	8.86	+1.88	17.46	67.1	69.3	155.0	1,455	960	3.5	3.5		
1/24/29	11.07	8.78	0.69	9.47	+1.60	17.46	69.2	69.4	171.3	1,642	1,120	5.0	5.6		
1/25/29	11.28	8.82	0.69	9.51	+1.77	17.58	70.5	69.4	200.5	1,757	1,430	5.5	7.4		
1/26/29	11.28	8.26	0.69	8.95	+2.33	17.69	70.5	69.4	200.5	1,757	1,080	5.0	5.4		
1/27/29	11.28	8.78	0.69	9.47	+1.81	17.58	70.5	69.4	200.5	1,757	1,170	8.0	9.4	No casts	
1/28/29	11.28	8.62	0.53	9.15	+2.13	17.80	70.5	69.4	200.5	1,757	1,140	8.0	9.1	No casts	
1/29/29	11.30	8.38	0.53	8.91	+2.29	17.92	70.0	69.4	194.5	1,755	1,125	5.0	5.6		
1/30/29	11.28	8.33	0.53	8.86	+1.42	17.92	70.5	69.4	200.5	1,757	1,350	7.0	9.5	No casts	
1/31/29	11.28	8.88	0.53	9.41	+1.85	17.46	70.4	69.4	200.5	1,756	1,155	8.0	9.2	No casts	
2/ 1/29	11.28	6.83	0.53	7.42	+3.76	17.80	69.9	69.4	200.5	1,755	970	4.0	3.9	No casts	Urine incomplete
2/ 2/29	11.30	7.44	0.66	8.10	+3.10	18.14	70.0	69.4	200.5	1,755	1,185	6.5	7.7	Few casts	
2/ 3/29	8.74	8.60	0.66	9.26	−0.52	18.26	54.6	47.4	177.0	1,392	1,570	7.0	11.0	Few casts	
2/ 4/29	7.66	6.73	0.66	7.39	+0.27	18.07	47.9	51.3	127.4	1,196	1,395	4.0	5.6	No casts	
2/ 5/29	10.04	7.77	0.66	8.43	+1.66	17.36	63.1	68.8	114.7	1,369	1,130	5.0	5.7	No casts	
2/ 6/29	10.35	7.98	0.66	8.64	+1.71	17.36	64.7	69.0	150.1	1,522	1,235	5.0	6.2	No casts	
Average	10.87	7.98	0.62	8.60	+2.07	17.92	66.7	68.0	155.0	1,543	1,337	6.2	8.3		

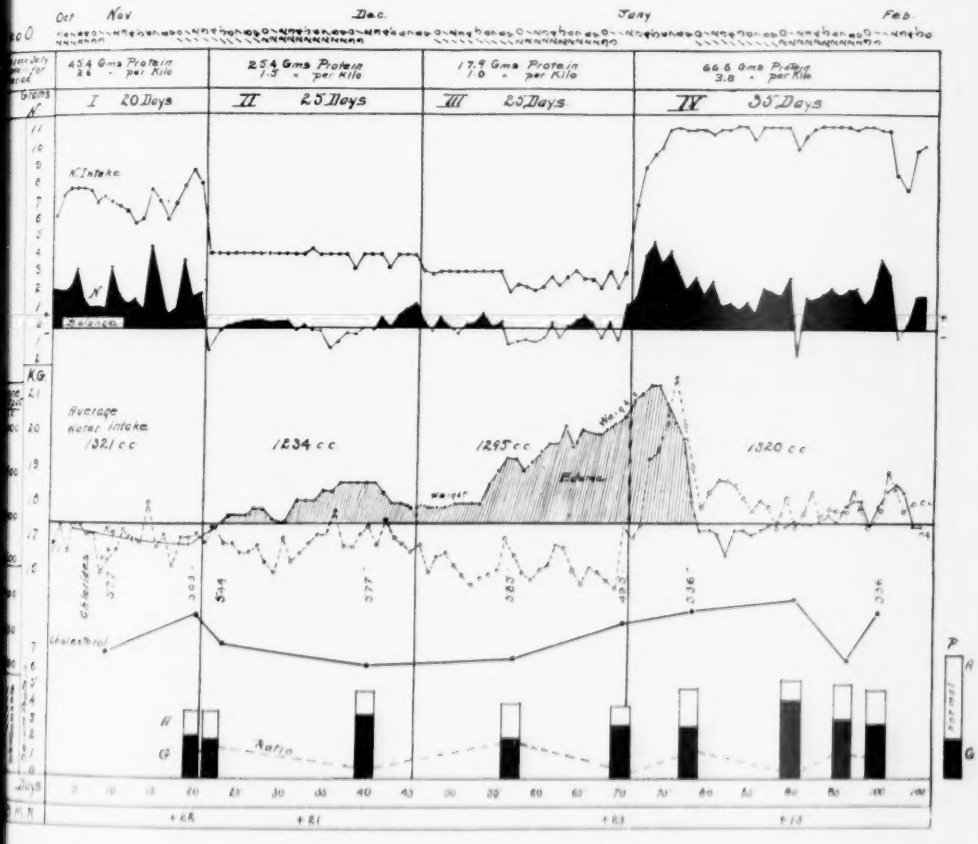
SUMMARY

Period	Number of Days	Dates Inclusive	Food: Carbohydrate	Fat	Protein	Protein, Gm. per Kg.	Calories	Calories per Kg.	Nitrogen Metabolism: Food Nitrogen, Gm.	Urinary Nitrogen, Gm.	Stool Nitrogen, Gm.	Total Nitrogen Output	Nitrogen Balance: Daily Nitrogen Balance, Gm.	Total Nitrogen Balance, Gm.*	Total Nitrogen Balance Expressed As Protein, Gm.	Urine: Cc.	Albumin Daily, Gm. per Liter	Albumin Absolute, Gm. per Day	Basal Metabolic, Rate per Cent
I	20	Oct. 25 to Nov. 13, 1928	126.0	74.9	45.4	2.6	1,339	80	7.28	4.81	0.58	5.39	1.87	36.79	229.9	795	4.5	3.6	+22
II	22	Nov. 14 to Dec. 5, 1928	230.9	59.5	25.4	1.5	1,194	68	4.06	3.27	0.66	3.93	0.13	2.84	16.7	783	6.3	4.9	+21
III	22	Dec. 6 to Dec. 27, 1928	272.2	60.9	17.9	1.0	1,346	77	2.86	2.28	0.53	2.81	0.05	1.84	11.8	507	8.2	4.2	+23
IV	20	Dec. 28 to Jan. 16, 1929	155.0	68.0	66.7	3.8	1,543	88	10.67	7.98	0.62	8.60	2.07	72.39	458.4	1,337	6.2	8.3	+13

* Total nitrogen balance for the entire period.



It appears that in this case a protein intake that is just adequate for the growing needs of the body was necessary to keep the albumin output at the lowest level (table 2); for when it was raised above this point more albumin passed the membrane. With the highest protein intake (the latter part of the fourth period) there was still practically twice the albumin output as compared with the first adequate period (period I). This occurred after adjustment had taken place and edema had dis-



Observations during four periods of study.

appeared. It is noted in the chart that during this time the nitrogen retention was the same as it was during the first edema-free period.

The Relationship of Nitrogen Retention to Edema.—During the first period of observation, the pre-edema period, while an average of 3.6 Gm. of albumin was still being excreted daily, 2.6 Gm. of protein per kilogram maintained a definite positive nitrogen balance, varying from 1 to 4.5 Gm. (chart, table 2). When the protein intake was lowered to an inadequate amount (1.5 Gm. per kilogram), edema devel-

oped, there being an insufficient number of food calories (average 1,200) to promote increase in weight and a tendency to a negative balance. When this protein intake was lowered still further, the edema gradually increased to three times its previous degree. When the protein was increased to the point of bringing about a positive nitrogen balance of 5 Gm., the edema promptly disappeared. From these observations, we believe we are justified in the statement that in this case a positive nitrogen balance of from 2 to 5 Gm. is incompatible with edema. On days when the balance reached + 1.5, there was a decrease in weight.

Effect of High Protein Intake on Nitrogen Retention in the Circulating Blood.—During the progress of these observations, nine non-

TABLE 3.—*Blood Chemistry*

Period		Date	Serum Proteins, per Cent	Serum Albumin, per Cent	Serum Globulin, per Cent	Ratio, Albumin to Globulin	Cholesterol, per Cent	Blood Chlorides, Mg.	Nonprotein Nitrogen, Mg.	Creatinine, Mg.	Serum Calcium, Mg.	Inorganic Phosphorus, Mg.	Sugar, per Cent	Nitrogen Balance
Edema free	I	Nov. 8	...	...	...	....	0.550	577	25.4	...	...	...	.....	+0.30
		Nov. 13	5.8	4.3	2.5	0.52	0.655	564	34.2	1.6	8.7	5.5	.....	+4.02
	II	Nov. 27	5.9	4.6	2.3	0.70	0.585	544	27.5	1.6	...	...	.....	.....
Edema		Dec. 4	5.0	3.3	3.7	0.55	0.525	577	24.8	1.6	7.8	3.4	.....	0.05
Edema	III	Dec. 21	4.3	1.9	2.4	0.80	0.535	585	20.7	1.5	...	...	.....	.....
Edema		Jan. 3	4.2	1.4	3.1	0.35	0.640	495	21.3	...	...	...	.....	.....
Edema free	IV	Jan. 11	5.1	2.1	3.0	0.70	0.675	536	36.4	...	9.5	5.5	0.082	+2.85
Edema free		Jan. 23	5.6	1.06	4.5	0.24	0.704	...	24.5	...	...	5.2	0.105	.....
		Jan. 29	5.4	2.1	3.3	0.64	0.529	...	....	...	...	...	0.082	.....
		Feb. 2	5.0	1.8	3.19	0.57	0.671	536	37.9	...	9.6	4.4	0.099	+3.56
Ascitic fluid		Jan. 11	1.5	...	...	....	0.030	660	35.1	...	7.4	...	0.110	

* Average, 0.54.

protein nitrogen determinations were made (table 3). The lowest value obtained was 20.7 mg.; the highest, 37.9; the average, 28.1. From these figures it is safe to say that there was no retention of nonprotein nitrogen in the blood itself, and that the kidneys were functioning normally in the excretion of uric acid, urea and creatinine. In other words, it is certain that the retained nitrogen during the two stages of marked positive nitrogen balance was to no great extent held in the blood.[5] During the observations, no tappings for ascitic fluid were done, because we did not want to interfere in any way with happenings that might be ascribed to influences other than the diet. After the weight had returned to normal and all visible evidences of edema and ascites had disappeared, we attempted to prove this by tapping. With difficulty,

5. The serum proteins were always below the normal figures, although they did show a definite increase during the high protein feeding.

enough peritoneal fluid was obtained for a test, which showed a nonprotein nitrogen of 35.1 mg. This, however, cannot be considered as representative of the ascitic fluid because of the unsatisfactory nature of the specimen. During the stage of marked ascites preceding the observations on the nitrogen balance (table 1), the nonprotein nitrogen of the ascitic fluid was 14.2 mg. It seems reasonable to say that there was no retention of nitrogen in the ascitic fluid because of the small quantity obtained at the end of the last period.

The retained nitrogen, we believe, is retained in protein storehouses in the same way as fat and carbohydrate are retained. This property of storage of nitrogen is well shown in unpublished studies from this clinic on nitrogen balance in children of preschool age by John P. Parsons.[6] Our observations confirm those of Mosenthal,[7] 1916, and illustrate very well his conclusion that discretion be exercised in interpreting a normal figure for nonprotein nitrogen of the blood as indicating that no nitrogen retention has taken place. They further show, as his observations did, that a positive nitrogen balance cannot be taken as an absolute indication that the kidneys are unable to excrete this substance.

Effect of Varying Protein Intake on the Nitrogen Content of the Stools.—Irrespective of the amount of nitrogen ingested by this patient, the absolute amount of nitrogen excreted in the stools (table 2) was quite constant (average, 0.58, 0.66, 0.53 and 0.62 Gm., respectively, for each feeding period). If we had calculated this loss of nitrogen in the stools on the basis of percentage of nitrogen intake, as is usually done, it would have seemed that the stool nitrogen varied considerably. This, however, was not the case, for with the constant stool nitrogen the percentage of nitrogen output was greatest on the lowest nitrogen intake. The estimation of the loss of nitrogen through the stools on the basis of percentage of nitrogen intake seems therefore to constitute a source of error in any experiments on nitrogen balance in which the protein intake is varied to any great extent.

Relation of Serum Protein to Edema.—Throughout the entire study of this patient during edema-free or edema periods, the serum protein has always been definitely below normal (table 3, chart). It has varied from 3.8 to 5.6 per cent. The globulin has always exceeded the albumin. The albumin-globulin ratio has varied from 0.24 to 0.80, the average of nine observations being 0.54. During the highest protein intake period, the serum protein showed a tendency to increase. The protein with the larger colloidal particles (globulin) was retained while the albumin

6. Parsons, J. P.: Nitrogen Metabolism of Children with Special Reference to the Protein Requirement of Children of Preschool Age, Am. J. Dis. Child. **39:** 1221 (June) 1930.

7. Mosenthal, H. O., and Richards, A. E.: Nitrogen Balance in Nephritis, Arch. Int. Med. **17:**329 (Feb.) 1916.

with the smaller colloidal particles passed the membrane into the urine. The highest serum protein was observed following the disappearance of the edema in the fourth period. The greatest change in the total serum protein during the entire investigation was 1.8 Gm. (3.8 to 5.6, table 3). The greatest increase in the albumin was 1 Gm. This occurred at the beginning of the second edema-free period. The greatest change in globulin was 2.2 Gm., in the middle of the last or highest protein intake and edema-free period. At this time the albumin-globulin ratio reached its lowest point and the urinary albumin had suddenly decreased more than half its previous amount. One is not justified from this study in placing any significance on these variations, as the method itself is not sufficiently accurate to permit one to make close distinctions.

It is of interest to note that a low serum protein with reversed albumin-globulin ratio was not incompatible with absence of edema. The question naturally arises: Is there any relationship between serum protein and the occurrence of edema? Peters [8] and his co-workers (eleven patients) showed that "with one exception edema is present in every instance in which the proteins are below 4 per cent,[9] and never is it observed when they exceed 5 per cent." Our case is in accord with the latter statement, and both statements are in accord with Linder, Lundsgaard and van Slyke,[10] who further pointed out that "in the glomerulo-tubular or nephrotic type, active or recently active, the total plasma proteins were less than 5 grams per 100 cc. This decrease from the normal (5.5 to 7.5) occurred whether the edema was present or absent. This affected chiefly the albumin. . . . The ratio of albumin was reduced to less than one and occasionally to 0.6." Our case is also in accord with this statement. Linder and his collaborators found that in severe cases of nephrosis the decrease in serum albumin was greater than it is in "nephrotic glomerular nephritis." The albumin-globulin ratio ranged as low as 0.26. In our case, the albumin-globulin ratio went as low as 0.24, and according to this point of view it would be regarded as a case of "severe nephrosis."

Leiter's [11] observations are of great interest at this point. He bled dogs twice daily, from 400 to 500 cc. of blood being obtained, and returned to the blood the corresponding volume of erythrocytes suspended in modified Locke's solution. Fifteen hundred cubic centimeters of 0.85 per cent sodium chloride solution was given daily by stomach

8. Peters, J. P.; Wakeman, A. M.; Eisenman, A. J., and Lee, C.: Pathogenesis of Nephritic Edema, Yale J. Biol. & Med. **1**:35 (Oct.) 1928.

9. Our very lowest protein reading, 3.8, was during an edema-free period.

10. Linder, G. C.; Lundsgaard, C., and Van Slyke, D. D.: The Concentration of Plasma Proteins in Nephritis, J. Exper. Med. **39**:887 (June) 1924.

11. Leiter, L.: Experimental Edema, Proc. Soc. Exper. Biol. & Med. **26**:173 (Nov.) 1928.

tube. Edema usually appeared in these animals about the fifth day; first in the soft tissues, then in the abdomen and chest walls. At the same time, ascites and hydrothorax developed. The edema rarely involved the fore limbs. It usually developed when the plasma proteins fell to 3 per cent or less, and receded with the rise of the plasma proteins above this level as a result of the discontinuance of the bleeding. The ascitic fluid protein content was often below 0.1 per cent. In previous experiments dogs that were bled without replacement of the erythrocytes did not show edema. It seems quite clear from the cases cited and from Leiter's experiments on dogs that reduction in serum protein has a great deal to do with the development of edema.[12] In the experiments on dogs, the cause of the lowered serum protein and how it is affected are clear. In our cases of nephrosis the cause is often clear—infection; how it operates is not so clear.

The Effect of High Protein Intake on the Serum Protein Content of the Blood.—As already stated, in our case the serum protein was consistently highest during the highest protein intake period, 70 Gm. per day. This protein intake did not produce significant changes in the serum protein. The slight increase that does occur is within the limits of error of the method employed. However, Fahr and Swanson[13] reported an increased serum protein when as high an intake as 200 Gm. of protein a day was ingested.

Osmotic Pressure.—Because of the marked loss of protein from the blood and because of the fact that the osmotic pressure of the blood protein is considerable, the question arises: Is the edema in this case due to a decrease in the osmotic pressure, the pull, of the plasma? By examining our protocols and by referring to the chart and table 3, it will be seen that the blood chlorides were almost always considerably above the normal range (from 450 to 500 mg.) and the blood sugar was never lowered. The osmotic pressure of the blood is believed to be due in greater part to its inorganic salt and organic crystalloid content, only to a slight extent to its colloid content. Accordingly, it seems that the edema in this case is not due to the decrease in the osmotic pressure of the blood caused by a loss of serum protein, as this loss is more than offset by the high level of the crystalloid content of the blood if we include the cholesterol. The chlorides of the ascitic fluid

12. Since the presentation of this paper, H. A. Christian (Nephrosis, J. A. M. A. **93**:23 [July 6] 1929) reported similar observations. The dogs developed edema, low basal metabolic rate, low blood protein with reversed albumin-globulin ratio and increased blood lipoids.

13. Fahr, G., and Swanson, W. W.: The Quantities of Serum Albumin, Globulin and Fibrinogen in Blood Plasma in Acute and Chronic Nephropathies, Arch. Int. Med. **38**:510 (Dec.) 1926.

at the end of the edema period were 660 [14] as against 536 mg. of the whole blood; the protein, 1.8 per cent as against 5.1 per cent. On another occasion when the ascites was marked, the chlorides of the ascitic fluid were 643 as against 393 of the blood (table 1). There is no consistent increase in the tissue fluid chlorides over those of the blood, and there is no significant passage of protein into the tissue spaces, if we regard tissue fluid and ascitic fluid as of approximately the same character. During a period of marked ascites prior to the beginning of these observations, the blood and ascitic fluid sugar were 0.105 and 0.104 per cent, respectively (table 1).

Cholesterol.—Throughout the entire study the blood cholesterol was high. It varied from its lowest point, 525 mg. per hundred cubic centimeters, during the first edema period, to its highest point, 704 mg. per hundred cubic centimeters, during the second edema-free period. In the chart it is seen to be gradually increasing through the edema period, and it continues to be high during the succeeding edema-free high protein feeding period. Maxwell [15] observed that much higher cholesterol values are found in chronic parenchymatous nephritis than in other forms and that "its increase is in no way proportional to the degree of edema." In acute nephritis during the recovery stage, he makes the observation that the edema first clears up, the plasma cholesterol next returns to normal and then usually becomes subnormal for a time, and lastly, the albumin practically disappears from the urine. In this case this sequence has not occurred after a period of eighteen months. In the stage of nephrosis the albumin output is higher than it is in nephritis. The same is true of cholesterol. A relationship between albumin loss from the blood and cholesterol increase is suggested. However, the variation in these factors during the entire period of observation we think was not of sufficient amount or permanency to enable one to say that increased blood cholesterol is a compensating mechanism. In May, 1928, the albumin loss was about 8 Gm. a day; the blood cholesterol was 580. In October, 1929, the albumin loss was 8 Gm. a day; the blood cholesterol was 550. If a time should come when the albumin loss is insignificant and the blood proteins return to normal, the question could be answered by a determination of the blood cholesterol.

Basal Metabolism (table 2, chart).—We record but one case. In other cases of similar nature we have found the basal metabolic rate characteristically low, as has been pointed out by Epstein and others.

14. It will be recalled that this specimen of ascitic fluid was unsatisfactory from the standpoint of chemical analysis.

15. Maxwell, J.: The Blood Cholesterol in Nephritis, Quart. J. Med. **21**:207 (Jan.) 1928.

In this case, the rate was persistently high: + 20, + 19, + 22, + 21, + 23 and + 13. The highest value was obtained on January 3, the first day of the high protein period, when the edema was at its highest point. Twenty days later, the edema had disappeared. The patient was still ingesting 70 Gm. of protein a day, and the rate was found to be at its lowest point, + 13. These observations were in all respects entirely satisfactory. Herein our case differs from the usual case of its kind. On two subsequent entries at three month intervals the basal metabolic rate was + 15 and + 7, respectively.

Calcium.—Unfortunately, we were unable to make more than four blood calcium determinations during the experimental period of this investigation. They were 8.7, 7.8, 9.5 and 9.6 mg. per hundred cubic centimeters, respectively. Only two of these were below the accepted normal (8.7 and 7.8). These occurred at a time when the serum protein was 3.8 and 5 per cent, respectively, and the daily albumin output was 3.6 and 5.4 Gm. From these four simultaneous determinations of serum protein, serum calcium (table 3) and urinary albumin (table 2) there seems to be no absolute correlation between lowered serum protein, lowered serum calcium and albumin output. There is, however, a tendency for a lowering of the serum calcium in the presence of a lowered serum protein.

There was a greater amount of urinary albumin during the first part of the highest protein feeding period (from 5.7 to 18.8, average 10.1 Gm.). At this time we might have expected a low serum calcium because from 40 to 50 per cent of the calcium is bound to the protein.[18] The blood calcium, however, was at its highest level at this time. This may be because the high protein diet has a tendency to restore normal blood calcium.

SUBSEQUENT PROGRESS NOTES

Third Admission.—June 4 to July 27, 1929: The patient returned to the hospital for removal of the tonsils and adenoids and for observation. In the interim of four months, he was kept on a general diet, containing approximately 60 Gm. of protein daily. He had been up and about, but had not been to school. His mother stated that his condition had been better than it had been for two or three years. There had been no return of edema, nor any appreciable gain in height or weight. During the past three weeks there had been a slight nonproductive cough, which had not limited his activities.

On June 4, the child measured 41 inches in height, weighed 38.5 pounds, and had a temperature of 99.8 F. (by rectum). His skin was tanned. The tonsils and adenoids were septic. Coarse moist bronchial râles were heard over the right side of the chest posteriorly; otherwise, the lungs were normal. The heart was normal, and the blood pressure was 120 systolic and 80 diastolic. The abdominal wall was still flaccid and there was no fluid. The liver and spleen were not felt. Edema was not noted.

18. Cramer, B.: Tr. Am. Pediat. Soc.; Am. J. Dis. Child. **38**:651 (Sept.) 1929.

The serum protein was 4.5 per cent; albumin, 1.6 per cent; globulin, 2.9 per cent; blood chlorides, 500 mg.; serum cholesterol, 0.438 per cent; serum calcium, 8.7 mg.; inorganic phosphates, 5.2 mg.; nonprotein nitrogen, 32.2 mg. The specific gravity of the urine was from 1.008 to 1.015; phthalein, 55 per cent; albumin, from 4 to 9 per cent daily; output, from 52 to 195 cc., with no cells or casts. The basal metabolic rate was +15 per cent.

Tonsillectomy and adenoidectomy were performed on July 8, 1929, with no untoward effects. There was no recurrence of edema during this period of hospitalization. The patient was discharged on July 27.

Fourth Admission.—Oct. 31, 1929, to Nov. 13, 1929: The patient returned to the hospital after an absence of three months. He had been in unusually good health until three weeks before when bronchitis developed. At the time of admission his condition had improved. During this illness, anorexia and vomiting developed. He lost weight, grew paler and had a severe nosebleed lasting forty-five minutes. He had an occasional dry cough. He had been on a general diet, eating meat twice daily, one egg daily, fish once a week, and an abundant amount of fruit.

His weight was the same as six months before. His height had increased slightly. He did not look ill. There was no evidence of edema. The abdominal walls were relaxed. Diastasis was still noticeable. There was no evidence of fluid. Slight bronchitis was noted. The heart was normal. The blood pressure was 122 systolic and 70 diastolic.

Examination of the blood showed: red cells, 4,100,000; white cells, 13,000; normal differential count; hemoglobin, 67 per cent; nonprotein nitrogen, 38.8 mg.; chlorides, 536 mg.; serum protein, 4.9 per cent; serum albumin, 1.9 per cent; serum globulim, 3 per cent; serum cholesterol, 0.55 per cent. Urinalysis showed: specific gravity, 1.008 to 1.015; albumin, from 2.26 to 8 Gm. daily; output, from 600 to 2,000 cc.; sediment, a few casts, and occasional red and white cells. The basal metabolic rate was +7 per cent on November 6.

The patient was discharged from the hospital on November 13, weighing 38½ pounds (17.5 Kg.).

Growth and Development.—When first seen, the patient weighed 57 pounds. After the edema fluid was removed (18 pounds), his net weight was 39 pounds (17.7 Kg.). In nineteen months his net weight had been reduced just one-half pound. This failure to gain was not due to an inadequate number of calories, excepting for the first low protein period of twenty-five days. During the last experimental period the caloric intake was 143 calories above his theoretical requirement (36 calories per pound), and since this time the calories have been maintained at about this figure. There is here seen a paradoxic reaction to food. The child is edema-free; he is satisfied with his food and occasionally consumes more calories than his diet calls for, but he fails to gain weight. During the nineteen month period he has gained 5 cm. in height, about 1.5 cm. less than the average normal child gains during this time. A moderate secondary anemia persists (4,100,000 red blood cells, 13,000 white blood cells and 67 per cent hemoglobin).

SUMMARY

We have presented what we regard as a case of chronic glomerular nephritis in a child, whose condition, under our observation, passed into the so-called nephrotic subgroup of glomerular nephritis, together with a detailed study of all the clinical factors, the blood and urine chemistry

and especially the nitrogen metabolism as influenced by changes in the protein content of the diet. The investigation was continued sufficiently long (105 days), without interruption or complications which might alter results, to justify definite conclusions.

We believe that our diagnosis of chronic glomerular nephritis is justified by the long continuance of symptoms of nephritis prior to their disappearance. Our diagnosis of nephrosis is based on the subsequent absence of the symptoms of a true nephritis over a long period of time and of the presence of the typical manifestations of nephrosis as delineated by Munk,[17] Volhard,[18] Fahr [19] and Epstein [20] and substantiated by Linder, Lundsgaard and van Slyke,[10] by Christian,[21] and by Murphy and Warfield.[22] Our diagnosis of nephrotic subgroup of chronic glomerular nephritis is based on the sequential changes we were fortunate enough to observe.

Edema and ascites in this case could be induced at will by feeding an amount of protein inadequate for the patient's nutritional needs, and likewise edema and ascites could be caused to disappear by feeding an adequate amount of protein. The amount of protein necessary to overcome and prevent edema was the amount [23] that would bring the patient into a positive nitrogen balance of from 1 to 3.76 Gm. and the blood proteins up to 5 Gm. per hundred cubic centimeters. A continuous nitrogen balance of from + 2 to + 5 Gm. was incompatible with edema. The feeding of protein in this amount was unattended by an increase in the nitrogen content of the circulating blood or the retained fluids of the body.[24] The retained nitrogen must therefore have been stored in some of the tissues, protein storehouses.

There is a definite relationship between the serum protein and edema. A serum protein below 4 per cent with a reversed albumin-globulin ratio

17. Munk, F.: Pathologie und Klinik der Nierenkrankungen, Vienna, Urban & Schwarzenberg, 1925.

18. Volhard, F.: Die doppelseitigen hematogen Nierenkrankungen, Berlin, Julius Springer, 1918.

19. Fahr, T.: Deutsches Arch. f. klin. Med. **125**:66, 1918; Virchows Arch. f. path. Anat. **239**:32, 1922; in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1925.

20. Epstein, A. A.: Concerning the Causation of Edema in Chronic Parenchymatous Nephritis: Method for its Alleviation, Am. J. M. Sc. **154**:638 (Nov.) 1917; Further Observations on the Nature and Treatment of Chronic Nephrosis, ibid. **163**:167 (Feb.) 1922.

21. Christian (footnote 12, p. 233).

22. Murphy, F. D., and Warfield, L.: Lipoid Nephrosis, Arch. Int. Med. **38**: 149 (Aug.) 1926.

23. 1.2 Gm. per pound, 2.6 per kilogram.

24. Frequent nonprotein nitrogen determinations were done. The average value was 28.1, the lowest 20.7, the highest 37.9. The nonprotein nitrogen of the ascitic fluid during a time of marked ascites was 14.2.

was not incompatible with the absence of edema in this patient. Edema was almost always present when the serum protein was below 4.5. A serum protein of 5 or above was never associated with edema. The albumin-globulin ratio in this patient went as low as 0.24. The serum protein was consistently highest during the periods of adequate and high protein feeding.

The edema in this patient cannot be ascribed to a lowered osmotic pressure of the blood. The chlorides were almost invariably above normal; there was no consistent increase in the ascitic chlorides, and the organic crystalloids were normal. The salt and crystalloid content of the blood more than offset the loss of colloid.

The cholesterol of the blood remained high throughout the entire study, and is still high (0.55 per cent) eleven months after the disappearance of edema. No definite relationship can be shown between cholesterolemia and edema in this patient.

A comparatively high protein intake [25] in this patient brought about an increase in the output of urinary albumin. The albumin output during the first fifteen days of the high protein feeding period was 150 per cent greater than it had been at the previous periods. At the end of this time, while the same amount of protein was being ingested, the albumin output became adjusted to a much lower level; but it continued to be approximately 50 per cent above the average amount for the previous feeding periods. Whether the high protein retention that occurred during this comparatively high protein feeding period really accomplished more in causing edema to disappear than a lower amount would have, we cannot say. The most spectacular urine output occurred on the seventh day of this period, after adjustment had taken place, and it carried away with it the bulk of the excessive amount of albumin. A comparatively high nitrogen retention in the tissues is compatible with considerable protein loss in the urine. There seems to be no definite amount of protein fed or of nitrogen retained with which the patient can be rendered albumin-free. There is always an albumin waste.[26]

The basal metabolism was consistently high throughout the 105 day study, whether there was edema or not. When it was highest, + 23, if we had calculated the rate on the actual tissue weight (body weight less weight of edema fluid) it would have been + 30. Herein our case differs from the usual one of its kind. Since the termination of these feeding observations, the basal rate has gradually returned to normal. Five months after the disappearance of edema it was + 15. Eleven months after it was + 7.

25. 1.7 Gm. per pound, 3.8 per kilogram.

26. Nov. 7, 1929, from 2.6 to 8 Gm. daily.

No constant relationship between serum protein and serum calcium or between albumin output and serum calcium was found.

It is demonstrated that in studies of nitrogen balance the actual chemical estimation of stool nitrogen is necessary in order to obtain an accurate figure for daily retention. The method of calculating the stool nitrogen as 10 per cent of the nitrogen intake is shown to be in error.

CONCLUSIONS

1. A case of chronic glomerular nephritis in a child whose condition, under observation, passed into the so-called nephrotic subgroup of glomerular nephritis is presented.

2. These studies demonstrate that in this case of nephrosis in a child characterized by a high metabolic rate, a protein intake sufficient to induce a positive nitrogen balance of from 1 to 3.76 Gm. was necessary and sufficient to keep the patient edema-free.

3. This amount of protein caused a marked diminution of the urinary albumin but it did not cause the albumin to disappear after a continuous edema-free period of eleven months.

4. A blood protein content of 5 Gm. was necessary before the patient became permanently edema-free. At one time the patient was edema free when the serum protein was 3.8 per cent.

5. In studies of nitrogen balance the actual chemical estimation of the nitrogen in the stool is shown to be necessary.

HELIOTHERAPY AND THE PERIPHERAL BLOOD*

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With the growth in popularity of the use of light treatment in disease, many claims have been set forth relative to the specific effect of irradiation on the human and the animal organism. A considerable amount of evidence has been collected indicating that light rays have a definite rôle in influencing metabolic processes, as witness the success with which the chemist has demonstrated their regulatory effect on calcium and phosphorus in rickets and tetany. Facts have, in the main, been obtained in the research laboratory. Owing to these observations, the clinician has been encouraged to enlarge the field in which heliotherapy can be used to advantage. Hence, light treatment has been enthusiastically applied in a group of diseases too large and well known to be mentioned here.

The result has been an abundant literature covering a wide field, in which claims are made of the beneficial effect of various forms of light treatment. There has been no clearcut experimental evidence, however, similar to that obtained by the chemist or the clinical investigator in calcium and phosphorus studies, to indicate how or through what physiologic channels these effects are produced. We felt that reports in the literature consisted mostly of hasty, incomplete and poorly controlled work. Laurens [1] in a comprehensive monograph and, more recently, Clausen [2] in a similar paper reviewed and commented on most of this work. We do not feel it necessary, therefore, to append a lengthy bibliography.

Since the introduction and exploitation of heliotherapy by Rollier, the outstanding enigma has been its effect on healing in tuberculosis of the bones and joints. This treatment has been used at the New England Peabody Home since the spring of 1914. Prior to the time the studies now being reported were commenced, no special attempt had been made to estimate the part played by sun treatment in the progress of the patients apart from any other factor. Owing to the sudden popularity

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1. Laurens, H.: The Physiological Effects of Radiation, Physiol. Rev. 8:1 (Jan.) 1928.

2. Clausen, Ethel M. Luce: The Therapeutic Value of Radiation, Medicine, 8:419 (Dec.) 1929.

that appeared a few years ago relative to the effectiveness of light per se in the treatment for disease, it was felt that we should attempt to demonstrate the presence of any specific effect that sunlight might produce in our patients. Hence, clinical studies were begun in the winter of 1927.

We decided to limit our observations to the study of changes in the peripheral blood that might occur as a result of light therapy. We thought that if it could definitely be shown that the various blood components were altered by irradiation, a start would have been made in detecting a definite vehicle by which physiologic changes occurred.

A group of children was selected on which frequent morphologic blood studies were to be made over a long period of time. Changes due to the influence of light were to be noted when the interval determinations were observed and compared. Forty children were chosen and divided into four equal groups. Group 1 was to receive direct rays of the sun, group 2 to receive sunlight behind ultraviolet ray transmitting glasses only, group 3 to receive mercury vapor quartz lamp treatment and group 4 to be kept in the open air without exposure to any form of direct light rays. The last-mentioned group (4) was intended to serve as a control group. Other factors entering into the treatment of the children, such as diet and orthopedic care, were standardized and similar in all groups.

The children we had to select from were patients being treated for, and in various stages of, tuberculosis of the bones and joints. Some of them had local lesions that were not causing any obvious systemic reaction. Lesions in others were of such a nature as to produce symptoms indicating varying degrees of constitutional disturbance. In a few instances, as time went on, evolution of the disease process caused a reversal of the initial condition. It was necessary to choose children for the study group with a view to having comparable factors relative to age, duration of disease, distribution of lesions and severity of symptoms. This was accomplished satisfactorily, considering the number of children available.

The ages ranged from 2 to 11 years. The average ages for the sun, window and air groups were nearly alike, i. e., about 6 years. The children in the lamp group were younger, averaging 4½ years of age.

Observations on the blood included determination of the hemoglobin content, the red blood cell count and the total white blood cell count with its differential picture, and determination of the ratio of the plasma and cellular elements of the blood, namely, the hematocrit reading. In order to minimize the effect of physiologic fluctuations in the values of these blood components at various times of the day ascribed to environmental factors and technical errors, two observations were made on each patient: one in the morning and one in the afternoon. A free flow of blood was obtained by the use of an automatic stylet, enabling simultaneous collection of blood for the various estimations. The blood pipets were calibrated and found to give consistent values. The Sahli method for measuring the hemoglobin was used. The hematocrit determination was obtained in two calibrated capillary tubes, centrifugated at a certain speed for a constant length of time, and the mean of the two readings taken as the true value if a difference was obtained. Cover-slip preparations with Wright's stain were used for differential purposes, and the Schilling-Torgau classification was used in making the counts. Determinations were made by one person throughout.

Observations were obtained through the study at quarterly intervals, as shown in table 1. Several determinations were made on each patient during each period. If a child showed any unusual deviation from normal, repeated determinations were made at once. This was in order to check any transitory fluctuation due to intercurrent infection or other untoward influence. The study was carried on over a period of two years and two months. Results are tabulated according to the nine periods into which this time is divided. This allows for comparison of values according to seasonal influences.

Our analysis of the data obtained has been made with a view to showing any possible correlation between the results of the study and the influence exerted by light. This necessitated arrangement of the data in group averages, as well as a study of the individual trend. The mean of the morning and afternoon determinations made on the day nearest the end of the period was used as the period value for each person. Space does not permit of including here the individual determinations from period to period.

TABLE 1.—*Periods During which Observations were Made*

1.	February, March, April, 1927
2.	May, June, July, 1927
3.	August, September, October, 1927
4.	November, December, 1927, January, 1928
5.	February, March, April, 1928
6.	May, June, July, 1928
7.	August, September, October, 1928
8.	November, December, 1928, January, 1929
9.	February, March, 1929

HEMOGLOBIN [3]

The average hemoglobin value for the group of forty children at the beginning of the study was 85 per cent. Individuals in the group showed the extreme limits of from 61 to 98 per cent. The average of the sun group was lowest (81 per cent) and that of the air group highest (88 per cent). The average of the lamp group was 86 per cent, and that of the window group, 84 per cent. Figures obtained during the second period showed a slight fluctuation in group values, but the average for all was 84 per cent. In the third period, which represented the advantage of spring-summer weather, there was an increase in all groups except the air group, the sun group particularly showing a striking increase. In periods 4 and 5, representing late fall to early spring, there was a tendency toward a slight falling off in values in each group except the air group. In periods 6 and 7, again representing the spring and summer months, there was a definite rise, followed again by a drop in the winter months.

3. It is generally accepted that the normal average hemoglobin content for children in the age group here represented is from 80 to 90 per cent by the method of Sahli.

This seasonal variation is most pronounced in the sun group; to hardly any extent is it discernible in the air group. The only explanation for this contrast between the two most vital groups seems to be that the children in the sun group happened to have, to begin with, low hemoglobin values as contrasted with those of the air group. Two of the children in the air group had values at the onset of 95 and 98 per cent, respectively. The three highest values in the sun group were 90 per cent; one child showed a value of 61 per cent. The existence of this variation was unexpected and unavoidable. When we selected the children for the various groups, the desired comparable factors seemed to exist.

Whatever reasons existed for these low hemoglobin values in the sun group, their influence evidently became less during the following two years, because the children having a low hemoglobin content at the beginning showed increases, and the children having a high hemoglobin content at the beginning showed little or no change. This was also true

TABLE 2.—*Hemoglobin Values for Each Group by Periods*

	Period								
	1	2	3	4	5	6	7	8	9
Sun	81	78	88	84	84	88	90	86	87
Window	84	83	88	85	86	91	91	87	94
Air	88	90	89	91	89	93	94	93	93
Lamp	86	84	89	85	85	88	91	89	87

of the air group. The fact is that a child with as high a hemoglobin content as it is logical for him to have refuses to be disturbed by any favoring influence. In a child having a subnormal hemoglobin, it is conceivable that any factor favoring betterment of his general condition will at the same time influence the hemoglobin content favorably.

The hemoglobin curve of the window group fairly well paralleled that of the sun group. The lamp group showed slight irregular fluctuations, but the values were neither high nor low. This group received throughout the seasons a heavy bombardment of ultraviolet rays.

It is interesting to note that the hemoglobin values for the air group were persistently the highest of all the groups. This was the control group which had been deprived of ultraviolet rays, except those obtained through skyshine. In looking to the individuals in this group for an explanation, we find that except for several of the children showing very high values, there is none to be offered. It is true that four cases in the group were ambulatory, but this fact has not apparently influenced their hemoglobin values.

We have attempted to evaluate any possible influence of light on these hemoglobin observations, and also to assign its proper rôle to each

of the other variables which exist and have an effect on the blood. We have found this a hopeless task. These other variables will be referred to later. Suffice it to say here that we are eliminating light as a sole factor in producing the changes observed in the blood.

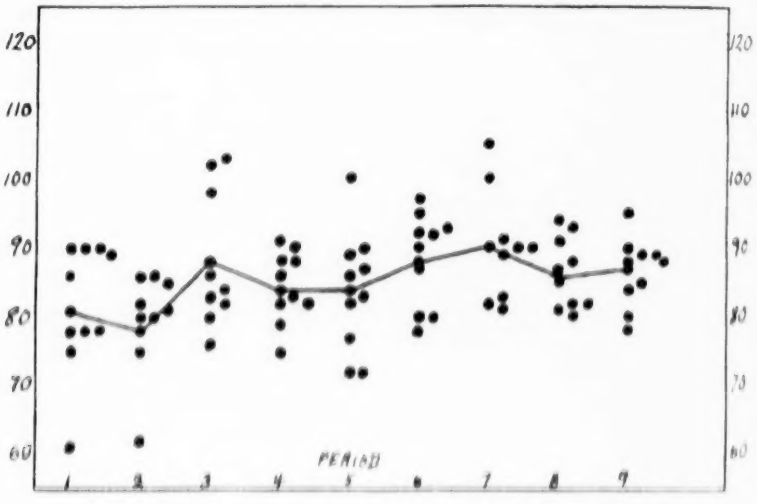

Chart 1.—The hemoglobin curve of the sun group. The individual values are plotted to illustrate the extreme variations which go to make up the average.

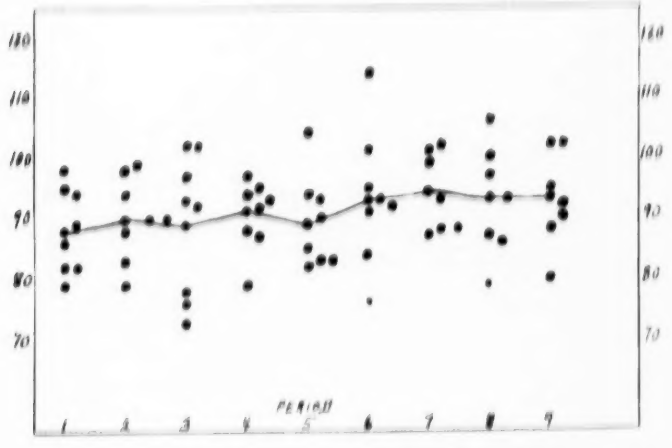

Chart 2.—The individual and average hemoglobin values for the air group.

The figures used in our charts were obtained from persons who showed meaningless fluctuations either during the day, from month to month, or from season to season; and even to try to establish some relationship between the hemoglobin values and those of the red blood cell

counts and hematocrit readings seems inconsistent. We must admit that there seems to be a slight tendency for the hemoglobin values to be higher in the summer months. However, with the lamp group showing the same tendency, it is unreasonable to try to ascribe this effect in the other groups to the influence of a greater number of ultraviolet rays. It would seem more logical to suggest that other beneficial attributes of the season are equally responsible.

RED BLOOD CELLS

We assume that the average normal red blood cell count for children of the age represented in this group is about 5,000,000 cells per cubic millimeter. At the onset of the study, the group averages were almost

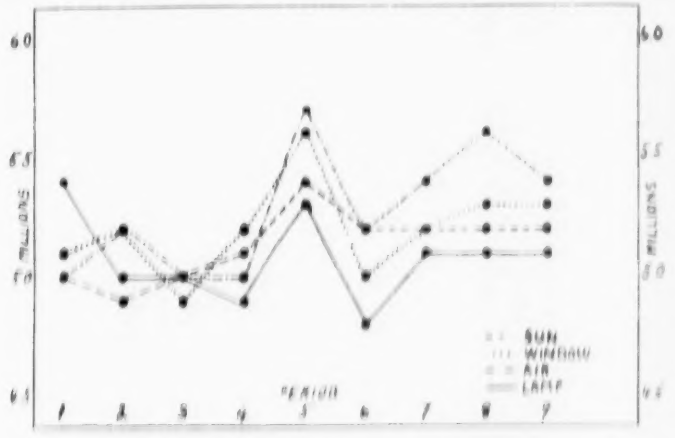

Chart 3.—Rise in the red blood cell counts in period 5.

identical and within normal limits. The individuals in the groups showed greatly contrasting values. Some were as low as 4,000,000, others as high as 6,000,000. In considering these children and the cause for such variation, we find that in most of them no ready explanation exists, so far as their general health and local disease is concerned.

The blood values showed no consistent or regular rhythm in their fluctuations. In period 5, which occurred in the late winter of 1928, there was a rather abrupt rise in the red cell counts, with a similar striking drop in the succeeding summer months. Chart 3 illustrates this. This rise anticipated that in the hemoglobin curves by an entire season. We find it impossible to ascribe any significance to this bizarre fluctuation. It did not consistently repeat itself the following year. Consequently, we must admit that the general trend of the red blood cell counts showed so slight a variation throughout the periods that

seasonal or other influences can be dismissed. Of course, it is true in certain children that improvement in general health had an effect.

HEMATOCRIT

We feel justified in including the hematocrit readings in our report, because they serve as still another indicator of changes occurring in the blood of these children. While the total quantity of blood in the body does not vary greatly, the concentration of its constituents is subject to a distinct change. In children with marked undernutrition or chronic diseases, when emaciation, anemia, etc., are present, the amount of solid constituents in the blood is found to be low. In states of hemorrhage, dehydration and shock, we are apt to find the reverse

TABLE 3.—*Red Blood Cell Averages for Each Group (in Millions) from Period to Period*

	Period								
	1	2	3	4	5	6	7	8	9
Sun	5.09	4.91	5.06	5.12	5.46	5.20	5.23	5.27	5.21
Window	5.16	5.22	4.91	5.25	5.61	5.02	5.23	5.36	5.32
Air	5.00	5.20	5.08	5.07	5.71	5.24	5.41	5.61	5.44
Lamp	5.44	5.04	5.01	4.95	5.33	4.80	5.14	5.11	5.18

TABLE 4.—*Hematocrit Averages from Period to Period*

	Period								
	1	2	3	4	5	6	7	8	9
Sun	33	37	41	39	37	39	38	39	37
Window	33	37	40	39	38	39	38	37	38
Air	37	40	43	40	40	41	41	40	38
Lamp	39	37	41	38	37	39	39	38	38

to be true. Hence, the hematocrit reading is a valuable aid in estimating the exact state of the circulating blood at a given time.

The hematocrit averages in these children were somewhat low at the beginning of the study. In the third period they showed an increase similar to that occurring in the hemoglobin curves. Throughout the rest of the periods the hematocrit reading closely followed the hemoglobin trend. As is to be expected from the behavior of the other blood components, the hematocrit reading was also somewhat higher at the end of the study.

WHITE BLOOD CELLS

The total white count showed marked variation in hourly, morning and afternoon and interval period determinations. The differential blood picture showed a similar temperament. This instability was general and very striking when the total counts or differential values were compared. For instance, a patient may have had a difference of

several thousand cells in morning and afternoon counts, although the differentials showed marked similarity. Again, the total counts may have been similar, while the differentials showed a change consisting of a transposition of the cells in their percentage distribution.

Average white counts for the groups throughout the study were strikingly similar. The individual variations, however, were great, ranging from 7,000 to 20,000 cells. For instance, one child in the sun group had a count of from 5,100 to 9,800, while another in the same group ran a count of between 14,400 and 23,000 cells.

In six of the nine periods, the sun and window group differentials were almost identical. The air group showed a higher polymorphonuclear cytosis in seven of the nine periods. The lamp group tended to

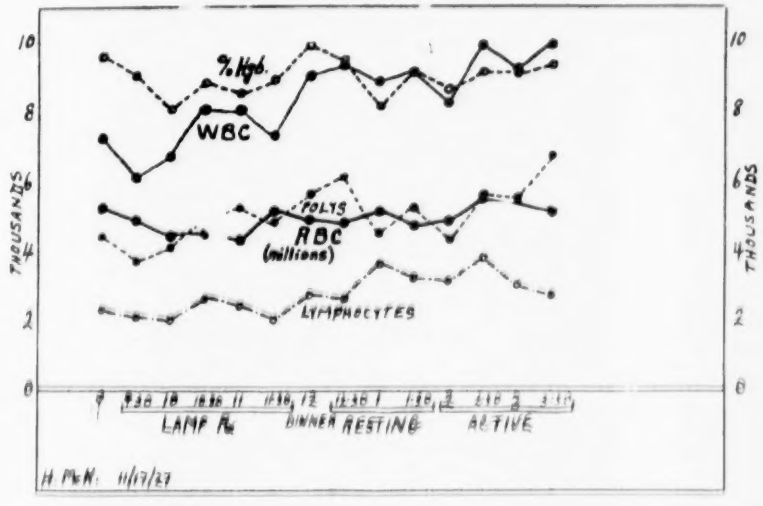

Chart 4.—Results of one of the special experiments performed on a child receiving intensive lamp treatment. This patient has a tuberculous spine, so far healed that he is ambulatory part of the time.

greater variations in the polymorphonuclear-lymphocyte ratio than the other groups, but with a grand average of 39 per cent lymphocytes. We do not consider these variations at all significant.

On the whole, the majority of these children showed a normal ratio between the lymphocytes and the polymorphonuclears, i. e., that expected in the healing or stationary phase of tuberculosis.

COMMENT

In presenting the figures obtained from our observations on the blood, we have pointed out that there are many factors that must be considered in interpreting results. In the first place, there is the

diurnal fluctuation in a person. It is not uncommon to find a child who shows a variation of from 5 to 15 points in percentage of hemoglobin between the morning and afternoon estimations. We wonder whether this tendency has been appreciated in general, and particularly by the observer who has attempted to draw conclusions from studies of the effect of heliotherapy on the blood. Also to be considered are the effect of food, fluid intake, physical activity, season of the year and any other stimulus or irritant.

In an endeavor to identify an influence that any of these factors might exert, we made observations on a few children at frequent intervals during the day, carefully noting just when these various agents came into play; i. e., blood was taken before breakfast, after breakfast, before, during and after exposure to light, during the rest hour, and so on, throughout the day. Chart 4 illustrates one of these special experiments. From all this maze of data we were unable to isolate any reaction in the blood picture that might be attributed to any of the aforesaid influences, either singly or collectively. All these factors come into play in a child's daily routine, and to try to single out cause and effect is impossible.

Again, as the observations from period to period are compared, there are at work other influences beside the amount of ultraviolet rays available that may produce a change. Here we must consider a local reaction to the disease process, its effect on the general constitution, the existence of times when current infection is being incubated or aborted or exists as a definite process; the presence of external irritants, which would include stimulation from many of the rays in the full range of the solar spectrum, and, finally, the physiologic changes occurring as the result of age and physical development.

CONCLUSIONS

1. There is no justification for the belief that light rays, considered either collectively as including the entire spectrum or individually as ultraviolet rays, have any specific effect on the blood.

2. The effect of light on the healing of a pathologic process, such as tuberculosis, cannot be distinguished from that exerted by other factors the beneficial influences of which are well recognized.

THE DIAGNOSTIC VALUE OF SODIUM FLUORESCEIN IN EPIDEMIC CEREBROSPINAL MENINGITIS *

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Sodium fluorescein is a dyestuff that has been used to determine the permeability of the meningeal barrier in health and in disease. The studies of Kafka,[1] Schönfeld,[2] Jervell [3] and others have established the fact that sodium fluorescein given by mouth in doses of about .3 Gm. per patient, or 0.030 Gm. per kilogram, will not permeate the meninges of the normal adult in two and one-half hours. In patients with meningeal disease permeation occurs in this length of time, as evidenced by the presence of the dyestuff in the cerebrospinal fluid. Jervell [3] employed this test in an investigation of the meningeal permeability of seventy-four patients, eighteen of whom were suffering from some form of meningitis, chiefly tuberculous meningitis. The dyestuff could be demonstrated in the cerebrospinal fluid of only those having meningitis. He concluded that the presence of sodium fluorescein in the spinal fluid within three hours after oral administration was indicative of meningitis, although it was not possible by this means to determine what form, and that inability to detect the presence of sodium fluorescein ruled out the disease. Schippers and Peters,[4] Esselbrügge [5] and Hamano [6] all agreed that the test was of distinct value in the differen-

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4. Schippers, J. C., and Peters, H.: Uranin as an Aid in the Diagnosis of Meningitis, Nederl. tijdschr. v. geneesk. **72**:4513 (Sept. 13) 1928.

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tiation of early meningitis from other diseases with meningitic symptoms. Hamano thought it positive only in well advanced meningitis.

So far, these investigations have dealt chiefly with tuberculous meningitis, syphilitic meningitis, purulent meningitis, meningism, serous meningitis and encephalitis. Few cases of epidemic cerebrospinal meningitis have been studied. Thus, Jervell reported no cases, while Schippers and Peters mentioned two and Esselbrügge, one. In all of these, the test gave positive results.

An epidemic of meningitis in Salt Lake City during the last part of 1928 and the first part of 1929 gave us an opportunity to investigate the value of sodium fluorescein as a diagnostic agent in a larger series of cases of epidemic cerebrospinal meningitis than any in which it has been studied heretofore.

METHODS

The dye was given by mouth or intramuscularly. In both instances, the dosage was the same, 0.025 Gm. per kilogram for infants and young children, and 0.030 Gm. per kilogram for older persons. When given orally, the sodium fluorescein was mixed with milk or marmalade, and the cerebrospinal fluid was removed at the end of two and one-half hours, by either spinal or cisternal puncture. With intramuscular injections, a 20 per cent solution was used, followed by removal of spinal fluid at the end of one-half hour. The latter method was feasible in most cases. Within a short time after injection, the patients became progressively yellow and then brown, the peak being reached at the end of four or five hours. Large amounts of the dye appeared in the excreta.

For reading the fluorescence of the spinal fluid, Jervell devised a box that he termed a fluoroscope, unfortunately, since this easily leads to confusion of it with the instrument used in roentgenology. It consisted of a dark box with a light shining into one end through a biconvex lens at a distance of 15 cm. from the tube containing the fluid to be tested. At the other end was an aperture for observation of the tube. Our dark box was essentially the same, except that the light was allowed to enter through the top of the tubes, one containing the spinal fluid and one containing water for a control. This simpler form of box served the purpose adequately. Readings were taken first with the undiluted fluid, and then with the fluid diluted until no fluorescence could be detected. It was found that thick, purulent fluids were sometimes difficult to read until centrifugated or allowed to settle; then readings of the supernatant portion were made.

Cerebrospinal fluids containing the dyestuff, sodium fluorescein, were characterized by the following observations: When small amounts were present, the fluid showed no fluorescence in the direct light, but when placed in the dark box a definite light greenish-yellow fluorescence was visible. Fluids containing higher concentrations of sodium fluorescein appeared yellow, and sometimes the fluorescence was apparent in direct light. When these fluids were placed in the dark box, they became a beautiful fluorescent opal color. The fluids were diluted with distilled water until the fluorescence disappeared. The last dilution in which fluorescence occurred was considered the end-point of the test, and this was designated by the number of dilutions. Thus the symbol four plus (4+) meant that the spinal fluid was fluorescent to and including the fourth dilution. Plus (+) meant that fluorescence could be demonstrated only in the undiluted spinal fluid. A dirty green color without fluorescence was found a few times. Jervell

considered this indicative of a minimum amount of sodium fluorescein. We found that fluorescence frequently became visible in such fluids after the removal of the thick fibrin and pus. Blood-tinged fluids, if positive, were considered so, since Jervell found that blood in amounts up to 0.33 cc. per ten cubic centimeters did not affect the readings. Our observations roughly substantiate this.

OBSERVATIONS

Table 1 records the results in thirty-three tests on twenty-one patients with clinically and bacteriologically proved epidemic cerebrospinal meningitis. In all but two cases, the sodium fluorescein test performed early in the course of the disease or before cure was established gave positive results.

In the first instance, the child (patient 15) was first seen nine hours after the onset of the illness with a chill, high fever and vomiting. On examination, the child was acutely ill, with a temperature of 103 F., 36 respirations per minute and a pulse rate of 140 per minute. A few indistinct petechiae were present over the abdomen and chest. The ophthalmologic observations were normal. The neck was slightly rigid, and there was a doubtful Kernig phenomenon. The knee jerks were somewhat exaggerated. The child was extremely irritable, but not more so than many children with high fever. The child was sent to the hospital with a diagnosis of probable meningitis, and on arrival, one hour later, there was no doubt about the diagnosis. Dark red petechiae were scattered over the skin surfaces, the neck was stiff and slightly retracted, there were positive Kernig, Oppenheim, Brudzinski and Gordon phenomena, and the tendon reflexes were greatly exaggerated. The temperature was 105 F.; the respirations were 56, and the pulse rate 160 per minute. In this short time, a change from an acutely ill to a moribund child had occurred. Puncture of the cisterna magna produced a clear fluid under greatly increased pressure, with a cell count of 12, negative reactions in the Pandy and sodium fluorescein tests, and no demonstrable organisms on smear or culture. Administration of serum was of no avail, and the child died twelve hours after the onset of the disease.

Although necropsy in this case could not be obtained, the history of the case was so like that characteristic of the fulminating type of meningitis seen during this epidemic that little doubt remained as to the diagnosis. This was undoubtedly an instance of death from fulminating meningococcus bacteremia. The absence of positive results in the globulin and sodium fluorescein tests indicates that the meningeal infection was of too short a duration and too slight a degree to give changes of the spinal fluid.

The second instance (patient 21) was nearly identical in every respect, except that the patient was 17 years old, and died twenty-eight hours after the onset of the disease. The spinal puncture was performed fifteen minutes after intramuscular administration of the sodium fluorescein. The fluid was clear and under considerable pressure, with a cell count of 25, a faintly positive Pandy reaction, and no evidence of sodium fluorescein. No organisms could be demonstrated at this time. Seven hours later, the spinal fluid was cloudy and under more pressure, and had a concentration of sodium fluorescein extending to six dilutions, a positive Pandy reaction and demonstrable meningococci.

TABLE 1.—*Observations in Twenty-One Cases of Epidemic Cerebrospinal Meningitis in Which the Sodium Fluorescein Test Was Used*

Patient	Age, Yr.	Weight, Kg.	Dose of Sodium Fluorescein, Mg. per Kg.	Spinal Fluid Changes: Character and Cell Count	Spinal Fluid Changes: Pressure	Spinal Fluid Changes: Pandy Reaction	Spinal Fluid Changes: Evidence of Sodium Fluorescein	Comment
1*	11	36	0.030	Cloudy	Moderate	+	3 +	
2	11	30	0.030	Very cloudy	Great	+	4 +	Second day
			0.030	Clear; 30 cells	Slight	—	—	Thirteenth day
3	2½	10	0.025	Cloudy and blood-tinged	Slight	+	4 +	Chronic meningitis one month
			0.025	Slightly turbid; 330 cells	Normal	Faintly +	+	Eighteen days later, clinically improved
			0.025	Turbid	Normal	+	15 +	Forty-five days later, posterior basic meningitis
4	9	25	0.030	Very cloudy	Great	+	4 +	Second day
			0.030	Very cloudy	Slight	+	0 +	Eighth day, clinically well
			0.030	Clear, 20 cells	Normal	—	—	Fourteenth day, no treatment since last test
5	3 mo.	5.5	0.025	Very cloudy	Moderate	+	2 +	Moribund
6	8	11	0.025	Cloudy	Moderate	Faintly +	1 +	First day
			0.025	Very cloudy	Normal	+ +	4 +	Sixth day, clinically improved
7	9	34	0.030	Cloudy	Slight	+	+	Fourth day
			0.030	Very cloudy	Slight	+	1 +	Seventh day
8*	7	23	0.030	Clear; 20 cells	Normal	—	—	Thirteenth day, clinically cured
9	12	50	0.030	Slightly cloudy; 360 cells	Moderate	+	1 +	Moribund
10	7	21.5	0.030	Very cloudy	Moderate	+	3 +	Second day
			0.030	Clear; 100 cells	Normal	0	+	Ten days later, clinically well; a few meningococci
11	13	43	0.030	Cloudy	Moderate	+	2 +	Sick 1 week; moribund
12	7	21	0.030	Cloudy; 1,200 cells	Moderate	+	+	First day
13	9	22	0.030	Cloudy; 30,000 cells	Great	+	1 +	Relapse after primary attack 3 weeks previously
14	2¼	11.5	0.025	Cloudy; 3,620 cells	Moderate	+	1 +	Second day
15	3	14	0.025	Clear; 10 cells	Great	—	—	Sick 8 hours; moribund; meningococcemia
16	18	50	0.030	Cloudy	Moderate	+	4 +	
17	20	55	0.030	Slightly cloudy; 450 cells	Slight	+	+	First day
			0.030	Blood-tinged	Slight	+	8 +	Fourth day
			0.030	Slightly cloudy	Normal	+	1 +	Seventh day
18	17	45	0.030	Blood-tinged	Slight	+ +	1 +	Fifth day
			0.030	Cloudy	Normal	+	+	Thirteenth day, seriously ill
19*	40	66	0.030	Cloudy	Great	+	8 +	Fourth day
			0.030	Clear yellow	Normal	—	—	Seventeenth day, cured
20*	42	64	0.030	Clear; 300 cells	Great	Faintly +	1 +	Second day
21	17	45	0.030	Clear; 25 cells	Great	Faintly +	—	Second day moribund; bacteremia

* Sodium fluorescein given orally. Spinal puncture at the end of two and one half hours.

Whether or not in the second case a puncture at thirty minutes would have shown a positive reaction for sodium fluorescein in the spinal fluid cannot be conjectured. The finding of the dyestuff after seven hours was of no diagnostic value, since it would appear in that length of time in a normal person.

The fact that the concentration of sodium fluorescein was slight in some cases (patients 12, 17 and 20), whereas after treatment the reactions became stronger, suggested the possibility of irritation by the serotherapy increasing the permeability of the meninges. The only other patients of this series whose cerebrospinal fluids gave negative sodium fluorescein reactions were examined by this means at a time

TABLE 2.—*Results of the Sodium Fluorescein Test in Cases* with Meningeal Symptoms That Were Not Cases of Meningitis*

Case	Age, Yr.	Weight, Kg.	Dose of Sodium Fluorescein, Mg. per Kg.	Spinal Fluid Changes: Character and Cell Count	Spinal Fluid Changes: Pressure	Spinal Fluid Changes: Pandy Reaction	Spinal Fluid Changes: Evidence of Sodium Fluorescein	Diagnosis
1	7	20	0.030	Slightly turbid; 50 cells	Moderate	Faintly +	—	Meningismic bronchopneumonia
2	3 mo.	5	0.025	Clear; 8 cells	Normal	—	—	Hypertonia
3	5	22	0.030	Clear; 10 cells	Slight	—	—	Meningismic erysipelas
4	9	30	0.030	Slightly blood-tinged; 420 cells	Great	+	—	Tetanus test made after antimeningococcic serum was given
5	2	12	0.025	Clear; 15 cells	Moderate	—	—	Spasmophilia
6	12	34	0.030	Blood-tinged	Great	+	—	Initial: epidemic encephalitis; final: tumor of the brain
7	5	18.5	0.030	Blood-tinged	Moderate	+	—	Meningismic bronchopneumonia

* In all these cases, the dyestuff was given intramuscularly, and the puncture was made at the end of one-half hour.

when they were clinically cured (patients 2, 4 and 8). An attempt was made to determine the value of the test in indicating the progress of the disease, that is, in indicating when it is safe to stop treatment. However, there was an insufficient number of instances of multiple determinations to allow a definite conclusion regarding this feature. Further studies in this respect will be made, if sufficient cases can be had.

The observations recorded in table 1 clearly indicate that a positive sodium fluorescein reaction was present in all but two uncured patients with epidemic cerebrospinal meningitis, and that in the case of these two there was a probable explanation for the negative observation.

Table 2 is a record of seven cases in which the test was of value in the differential diagnosis of meningitis. In all of these, signs of meningeal irritation were present, which in the presence of an epidemic of meningitis made the urgency of diagnosis all the greater. In the

case of patient 1, the intern administered antimeningococcic serum, irrespective of the fact that there was no evidence of changes in the spinal fluid. This act further complicated matters, for the reaction to the serum caused slight turbidity of the fluid at the next puncture. The absence of sodium fluorescein was sufficient evidence of the lack of meningeal irritation to give us courage to wait a few hours, after which definite signs of pneumonia could be demonstrated. In the case of patient 2 there was a history of convulsions prior to admission to the hospital and a diagnosis of possible meningitis by a competent physician to cloud the issue. Here, again, the sodium fluorescein test was of distinct value. In the case of patient 4, no test was made at the time of the first puncture, but because the symptoms of meningitis were so apparent, serum was administered. At the next puncture, the fluid was under increased pressure, but the sodium fluorescein reaction was negative, although there was a cell count of 420 and a positive Pandy reaction. Shortly afterward tetanus became apparent and the case was so diagnosed. In the case of patient 7, although signs of pneumonia were present at the initial examination, the manifestations of meningeal irritation, vomiting, rigidity and retraction of the neck and the Kernig phenomenon were so pronounced that meningitis had to be considered, too. Although the Pandy test was positive, and the pressure of the fluid increased, we felt that the absence of sodium fluorescein in the spinal fluid was sufficient to make the presence of meningitis unlikely. This case occurred at a sufficiently late period in the course of our study to make us feel extremely confident of the reliability of the test.

COMMENT

Ordinarily, the finding of blood in the spinal fluid at puncture makes the fluid nearly valueless for diagnosis. The failure to detect sodium fluorescein in such fluids is of distinct value in ruling out the presence of meningeal permeability of sufficient degree to make a diagnosis of meningitis. As has been shown by previous observers (Jervell) and substantiated by us, small amounts of blood, up to 0.33 cc. per ten cubic centimeters, do not invalidate the test. The Pandy test runs parallel with the sodium fluorescein test, or nearly so, but here again the presence of a slight amount of blood that will cause a positive Pandy reaction will not affect the result of the sodium fluorescein test. Therefore, one of the chief advantages of this test is that it enables one to determine the presence of meningeal inflammation in the presence of blood-tinged spinal fluid. According to Jervell, the cerebrospinal fluid in this test gives the characteristic greenish fluorescence of sodium fluorescein up to dilutions of 1 in 10,000,000. Schippers and Peters measure the sodium fluorescein content of the cerebrospinal fluid quantitatively, and regard concentrations greater than 0.04×10^{-5} indicative of meningeal disease.

Sodium fluorescein is nonpoisonous, and should not be confused with uranium, which is destructive to the tissue of the kidneys especially. In this study, an abscess occurred at the site of injection in one patient. This was probably due to the subcutaneous rather than to the intramuscular injection of the dyestuff.

CONCLUSIONS

1. A study of the value of sodium fluorescein as a diagnostic agent in epidemic cerebrospinal meningitis is presented, with two tables of the observations in thirty-three examinations in twenty-one cases.

2. Ingested or injected sodium fluorescein permeated the meningeal barrier in all but two uncured patients with clinically and bacteriologically diagnosed epidemic cerebrospinal meningitis. A probable explanation for the failure of the test in these two patients is proffered.

3. The test is of value in the differentiation of epidemic cerebrospinal meningitis from other diseases in which sometimes there are manifestations of meningeal irritation, such as pneumonia, erysipelas, spasmophilia, encephalitis, tumor of the brain and tetanus.

4. The presence of small amounts of blood does not invalidate the test, which makes it especially valuable in the diagnosis of meningitis.

ACUTE SUPPURATIVE THYROIDITIS IN CHILDREN

OPERATIVE RECOVERY *

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Acute suppurative thyroiditis in children appears to be extremely uncommon. Accurate statistics as to its frequency are lacking. In the better known monographs on the thyroid gland and in the various treatises on surgery and pediatrics, it is dismissed with a brief statement as to its extreme rarity and grave prognosis. For example, Means and Richardson [1] stated that "in young children acute thyroiditis is ordinarily fatal," while in another paragraph they said that "suppurative thyroiditis may lead to serious complications and even death through mediastinitis, perforation of trachea or esophagus, or from associated edema and pressure."

The literature pertaining to the condition is relatively barren. Demme [2] was reported to have seen congenital strumitis in a new-born infant. Burhans,[3] in a recent compilation of the reports of sixty-seven cases of acute thyroiditis from the recent literature, found two patients between the ages of 1 and 10 years, one of whom was 18 months old. No data were given as to the type of inflammation and the treatment given. Baratta [4] reported a case in an infant, aged 2 months, with marked pressure phenomena, in which relief was obtained by repeated aspiration.

In a previous communication, I [5] pointed out that acute inflammatory lesions of the thyroid gland are nearly always secondary to acute infections elsewhere in the body, the latter being most commonly situated in the upper or lower respiratory tract. In the cases here reported the

* Submitted for publication, March 1, 1930.

* From the Surgical Service of Dr. H. M. Richter.

1. Means, J. H., and Richardson, E.: Diseases of the Thyroid Gland, Oxford Monographs, London, Oxford University Press, 1929, pp. 346 and 348.

2. Demme, quoted by Crotti, Andre: Thyroid and Thymus, Philadelphia, Lea & Febiger, 1922.

3. Burhans, E. C.: Acute Thyroiditis, Surg. Gynec. Obst. **47**:478, 1928.

4. Baratta, A.: Raro caso di tiroidite acuta suppurativa in una bambina di due mesi, Pediatria **36**:602 (June 1) 1928.

5. Mora, J. M.: Acute Thyroiditis, Am. J. M. Sc. **177**:99 (July) 1929.

original infection was a sore throat, and in the first instance there was an accompanying bronchopneumonia.

Because of the rarity of the condition and the striking improvement that followed incision and drainage (which I feel is the logical treatment), the following cases were considered worthy of record. The first child is apparently the youngest in whom operative recovery has been reported.

REPORT OF CASES

CASE 1.—D. B., aged 2½ years (referred by Dr. J. K. Calvin), had been ill for six days before admission with sore throat, respiratory difficulty (primarily inspiratory) and fever. On admission, the temperature was 104 F., and the respiratory difficulty was marked, with some supraclavicular, infraclavicular and epigastric inspiratory retraction. The temperature soon became septic, varying from 99.5 to 105 F. daily. Clinically the picture was that of diffuse bronchitis with no physical evidence of pulmonary consolidation. The roentgenogram, however, revealed diffuse bronchopneumonia. Swelling in the region of the thyroid isthmus was first noted six days after the child's entrance to the hospital. This mass rapidly increased in size; dyspnea became marked, and the temperature remained septic. The leukocyte counts on two occasions were 24,000 and 26,500, the polymorphonuclears varying from 67 to 74 per cent. The patient was transferred for operation.

The mass was incised and drained through a short transverse incision made under light ethylene anesthesia. A large amount of pus and some necrotic thyroid tissue were liberated, which on smear and culture showed pure hemolytic streptococci. Examination showed the trachea to be extensively denuded and much of the thyroid tissue destroyed. The leukocytes numbered 11,600 twenty-four hours after operation. The child was discharged within a week in good condition.

CASE 2.—J. L., aged 13, referred by Dr. Abram Levinson, became ill five days before admission with sore throat, "swollen glands beneath the chin" and fever. One day after the onset of the condition, swelling over the thyroid was noticed, with moderate pain and some difficulty in swallowing. The mass gradually increased in size and became red and very sensitive. The child continued to have fever. On his admission, his temperature was 101.4 F., and his pulse rate 120. There was a fair-sized, sensitive, red, fluctuant mass in the region of the thyroid. The leukocytes numbered 17,950, with 92 per cent polymorphonuclears.

Under light nitrous oxide oxygen anesthesia the mass was incised and drained through a short transverse incision, a large amount of pus being liberated. Examination revealed the isthmus to have been chiefly involved, both lateral lobes being enlarged but not involved in the suppurative process. Bacteriologic examination disclosed a short chain hemolytic streptococcus. The child was discharged the following day, greatly improved.

COMMENT

These children will be watched for evidence of hypothyroidism, since it is known that acute inflammatory lesions of the thyroid frequently lead to destructive changes in the thyroid parenchyma.[6]

6. Hallberg, C. A.: Thyroiditis, Ann. Clin. Med. **1**:261, 1923.

Statistics on the mortality are lacking because of the paucity of recorded cases. It is significant that of forty-one adults with suppurative thyroiditis whose cases were reported by Robertson,[7] nine died (21.9 per cent).

SUMMARY

Two unusual cases of acute suppurative thyroiditis in children aged 2½ and 13 years, respectively, with operative recovery, are recorded. In both cases the primary infection was a sore throat, and in both instances the offending organism was a hemolytic streptococcus.

7. Robertson, W. S.: Acute Inflammation of the Thyroid Gland, Lancet 1:930, 1911.

A NEW INFANT FEEDING CHART*

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OWOSSO, MICH.

The accompanying chart was devised to make more complete and accurate the nurses' chart of feeding cases and to present to the physician on his rounds a rapid method of determining the progress of his patients not only for the previous day, but for an entire month. By glancing along a line, the physician can note the condition of the patient in a few seconds, while with the older method, several minutes were needed to examine a number of sheets for the same facts. Moreover, it has been my experience that if nurses are given a blank page, as a rule they will not always note the things that the physician wants to know, while if there is a specific space to be filled out, they will usually do so. With the older charting system, if the child stayed in the hospital for several months, the chart resembled a dictionary in size, while with this method, only one sheet a month is used. The saving in paper is obvious. The saving in nurses' time is also considerable, so that more time can be given to the actual care of the infant. After several months' use in the Children's Department of the Memorial Hospital the method has been satisfactory, and there is a desire on the part of those who have prepared the chart to extend the method in a modified form to other departments.

The date is at the right hand side of the sheet, and charting is begun on the day corresponding to the date of admission. The number of days in the hospital can easily be computed by counting the number of pages on the chart. The weight is charted on the lines given to it, suitable figures being placed in the spaces at the top, and the actual weight being written in the column at the extreme left. In the section headed "Oz. per Feeding," there are eight columns so that either a three or a four hour schedule may be used. The formula is written in the spaces provided: so many ounces of milk, water, lactic acid, if any, carbohydrate and, if wanted, other things may be entered in the "additional" column, such as orange juice, egg yolk, cereal or vegetable. The total number of ounces taken, multiplied by the calories per ounce of

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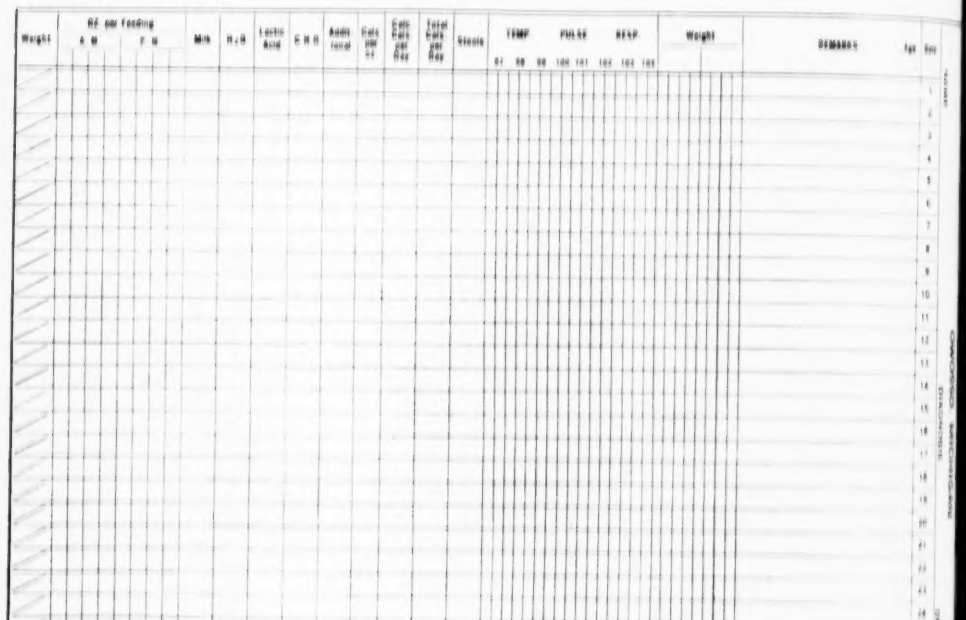
* From the Memorial Hospital.

the mixture used, gives the total number of calories per day, which is checked against the number of calories calculated on the basis of age and weight. The stools are charted by abbreviations, such as "n" for normal, "c" for constipated, "l" for liquid and so on, the number of day stools being written in black ink in the upper part of the space,



New infant feeding chart.

and the number of night stools in red ink in the lower part. The temperature is charted by a continuous line, while the pulse rate and respirations are written in figures. The remarks need be very brief, as most of the important information is already contained in the appropriate columns.

820 North Shiawassee.

DIFFERENTIAL WHITE COUNT IN INFANCY

COMPARISON BY SUPRAVITAL AND FIXED SMEAR METHODS *

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Discrepancies in the differential count of the white corpuscles are at once evident when counts made from the supravital preparations are compared with those made from fixed smears. The difference usually rests in the lower polymorphonuclear neutrophil and higher lymphocyte percentage of the fixed smear. The predominance of lymphocytes in the differential white blood count has always been regarded as characteristic of the blood of the normal infant following the first two weeks of life. This evidence has in general been based on the results of counts made from the fixed smear. At times, a routine fixed smear reveals a lymphocyte count out of all proportion to the clinical picture, and a presumptive diagnosis of a blood dyscrasia is entertained.

As the supravital technic provides a means of studying living blood cells with a minimum of trauma, differential white counts obtained by this method are more accurate than those utilizing some modification of the Romanowski stain. The present study was undertaken with the object of determining the extent of these differences in infants under 1 year of age. The investigation embraces the results of differential white blood counts in thirty-seven infants and includes both a normal group and one representing some pathologic condition. In all, forty-eight counts were made, and of these thirty-four constituted a combined examination of supravital preparation and fixed smears employing both coverslip and slide methods. In the remaining fourteen, a supravital count was compared with one type of fixed smear. The infants designated as normal came from the wards of the hospital prior to placement by the Foster Home Department. Although usually not up to average weight, they were free from infection, and the Mantoux tests, including tests with 2 mg. tuberculin, were negative.

METHOD

The procedure in a typical case included the following steps: Deep puncture of the heel was made to obtain a free flow of blood. Two drops were discarded, and in rapid succession blood was drawn for a total white count, for slides and a pair of coverslips for the Wright's stain and for the supravital preparation. For the

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* From the Department of Pediatrics, Cornell University Medical College, and the New York Nursery and Child's Hospital.

latter, the method developed by Sabin[1] was employed, and for details of the technic as well as the recognition of the different types of cells by this medium, reference is made to that author's papers. Scrupulous attention was paid to the cleanliness of the glassware, reaction of the alcohol and thickness of the smear. Vital neutral red alone or in combination with the vital Janus green to bring out the mitochondria were used in concentrations tested out to be nontoxic to the infant's white cells. These preparations were placed in the warm-box, kept at 37 degrees and allowed to remain in contact with the dyes for from twenty to thirty minutes before examination, so as to assure an adequate staining of the cells, particularly the monocytes.

In the average case, at least 200 cells were counted from each coverslip of the fixed smear and 300 from the supravital preparation, counts being made as far as possible from edge to edge. With the stained slides of the fixed smears, a minimum of 300 cells was counted, an average being taken of 100 cells each from the middle of the film, from the edges and along vertical lines crossing the entire width of the slide, the latter advised by Gyllensward[2] to reduce the sources of error resulting from the unequal distribution of the cells.

RESULTS

To simplify the recording of the observations, large, intermediate and small lymphocytes were grouped together, although the small variety of cell constituted the largest component. The monocytes are the cells formerly regarded as the transitional cells of Ehrlich, but through the studies of Schilling,[3] Naegeli[4] and Sabin,[5] they are now recognized as a strain distinct from the polymorphonuclear leukocytes and lymphocytes. The occasional clasmatocyte was more readily identified in the supravital preparation than in the fixed smear.

As will be discussed later, the fixed smears often contain white cells in all stages of disintegration, such as stained masses of débris probably once integral parts of a cell, free nuclei and fragile cells the membranes of which have ruptured but can still be classified. In these studies wherever the damaged cell or isolated nucleus could be at all identified, it was included with the appropriate cell group. There were at times, however, considerable numbers of free nuclei and smudges that could

1. Sabin, F. R.: Studies of the Living Blood Cells, Bull. Johns Hopkins Hosp. **34**:277 (Sept.) 1923.

2. Gyllensward, C.: Sources of Error in Differential Count of White Corpuscles in Stained Blood Smears, Acta paediat. **8**:1 (March 6) 1929.

3. Schilling, V.: Der Monozyt in trialistischer Auffassung und seine Bedeutung im Krankheitsbilde, Med. Klin. **22**:563 (April 14) 1926.

4. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 4, Berlin, Julius Springer, 1923, p. 141.

5. Sabin, F. R.; Doan, C. A., and Cunningham, R. S.: Discrimination of Two Types of Phagocytic Cells in the Connective Tissues by the Supravital Technique, Contrib. Embryol. 361, Carnegie Inst., Washington **16**:125, 1925; The Development of Leucocytes, Lymphocytes and Monocytes from a Specific Stem-Cell in the Adult Tissues, ibid., p. 227.

not be classified, which were omitted from the differential count. There is no doubt that if these stained masses were included, the discrepancy between the counts in the two types of blood smears would be greatly reduced. In this work, no systematic study was made of the maturity of the granulocytes in accordance with the Schilling index.

The blood was usually obtained in the afternoon, as indicated in the tables. Sabin, Cunningham, Doan and Kindwall,[6] in studying the rhythm of the various types of white cells in the normal adult person found that the total white count at any one time may be approximately twice that taken at another period of the same day. The higher counts occurred in the afternoon, and were independent of the ingestion of food. Fletcher and Mitchell[7] also observed an afternoon leukocytosis in a small group of infants and children. The leukocytosis in the normal infants noted in cases 3, 17 and 18 of table 1 may, perhaps, be accounted for on the same basis.

With the exception of case 8 (table 1) and cases 1, 4, 11 (second count) and 13 of table 2, the higher polymorphonuclear and lower lymphocyte percentages of the supravital preparations as compared with the fixed smears are clearly in evidence. The quantitative differences among the cell groups in the differential counts, however, show extreme variability. On the one hand, in case 2 (table 1) there are but 3 per cent more neutrophils and 1 per cent less lymphocytes in the supravital preparation than in the fixed smear. Case 15 (table 1), on the other hand, shows 70 per cent lymphocytes on the coverslip with Wright's stain as compared with 50 per cent in the differential count of the living cells. A discrepancy such as this illustrates the necessity for taking the entire clinical picture into account before an abnormal blood condition is considered.

In the pathologic group similar differences are encountered. In case 1 (table 2), the neutrophilic percentage is the same in both living and fixed smears. Case 7 (table 2), that of an infant with an enlarged mediastinal shadow, illustrates in marked degree the higher polymorphonuclear and lower lymphocyte percentages of the supravital differential count. Of course, with an overwhelming infection of pyogenic origin in which an outpouring of polymorphonuclear neutrophils into the peripheral blood takes place, the possibility of a marked discrepancy in the percentage of this type of cell in the differential count by the two methods is reduced. This is manifest in case 16 (first count), in table 2.

6. Sabin, F. R.; Cunningham, R. S.; Doan, C. A., and Kindwall, J. A.: The Normal Rhythm of the White Blood Cells, Bull. Johns Hopkins Hosp. **37**:114 (July) 1925.

7. Fletcher, E. G., and Mitchell, A. G.: Physiologic Variations in the Leukocytes in Infants and in Children, Am. J. Dis. Child. **34**: 807 (Nov.) 1927.

TABLE 1.—*Group of Normal Cases*

Case	Age	Time	White Blood Count	Percentages from Supravital Film					Percentages from Fixed Smears									
									Coverslip					Slide				
				Neutrophilic Leukocytes	Eosinophilic Leukocytes	Basophilic Leukocytes	Lymphocytes	Monocytes	Neutrophilic Leukocytes	Eosinophilic Leukocytes	Basophilic Leukocytes	Lymphocytes	Monocytes	Neutrophilic Leukocytes	Eosinophilic Leukocytes	Basophilic Leukocytes	Lymphocytes	Monocytes
1	2 weeks	4:45 p.m.	11,800	48	3	0	47	2	..	..	..	..	..	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
2	2 weeks	4:00 p.m.	8,000	42	1	0	56	1	..	..	..	..	..	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
3	1 month	4:50 p.m.	25,500	48	1	0	47	4	46	0	0	50	4	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
4	1 month	12:20 p.m.	20,200	47	6	0	46	7	33	3	0	57	7	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
5	6 weeks	5:00 p.m.	20,800	29	5	1	62	5	20	2	1	73	4	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
6	7 weeks	4:45 p.m.	7,600	33	10	0	65	2	19	0	0	79	2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
7	2 months	12:30 p.m.	7,700	34	6	0	50	10	27	5	0	60	8	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
8	2 months	5:00 p.m.	9,500	38	7	0	47	8	30	4	0	61	5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
9	2 months	2:30 p.m.	6,000	20	1	0	75	4	23	1	0	70	6	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
10	2 months	5:00 p.m.	9,800	48	1	0	51	0	..	..	..	..	..	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
11	2½ months	4:00 p.m.	17,500	37	10	0	48	5	33	4	0	58	5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
12	2½ months	4:30 p.m.	8,800	33	7	0	56	2	..	..	..	..	..	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
13	3 months	12:30 p.m.	12,500	37	5	0	51	7	33	3	0	58	6	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
14		4:20 p.m.	12,200	24	4	0	64	8	20	3	0	68	4	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
15	3 months	5:00 p.m.	7,200	41	1	0	56	2	27	0	0	70	3	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
16	4 months	11:45 a.m.	7,000	47	1	0	43	9	45	1	0	48	6	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
17		5:45 p.m.	8,400	58	0	0	34	8	49	0	0	46	5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
18	4 months	1:30 p.m.	6,600	37	7	0	50	6	32	5	0	70	3	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
19	4 months	3:50 p.m.	20,600	19	5	0	71	5	19	0	0	76	5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
20	5 months	4:15 p.m.	15,000	52	4	0	41	4	45	1	0	50	4	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
21	6 months	4:15 p.m.	26,000	35	1	0	61	3	20	0	0	76	4	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
22	8 months	11:30 a.m.	11,500	41	7	0	49	3	31	1	0	66	2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
23	8 months	4:45 p.m.	10,800	35	3	0	55	7	26	1	1	68	4	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
24	11 months	4:30 p.m.	12,600	30	10	0	54	6	24	10	0	62	3	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Average			10,173	37.9	3.9	0.04	53.3	4.9	29.3	2.2	0.1	63.9	4.5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

* In these cases both observations were made on the same or on the following day.

TABLE 2.—*Group of Pathologic Cases*

* In these cases both observations were made on the same or on the following day.

TABLE 2.—*Group of Pathologic Cases*

Case	Age	Diagnosis	Date	Time	White Blood Count	Percentages from Supravital Film: Neutrophilic Leukocytes	Eosinophilic Leukocytes	Basophilic Leukocytes	Lymphocytes	Monocytes	Percentages from Fixed Smears: Coverslip: Neutrophilic Leukocytes	Eosinophilic Leukocytes	Basophilic Leukocytes	Lymphocytes	Monocytes	Slide: Neutrophilic Leukocytes	Eosinophilic Leukocytes	Basophilic Leukocytes	Lymphocytes	Monocytes
1	10 mo.	Tuberculosis of bones and skin	3/ 5	11:30 a.m.	19,600	64	1	0	26	9	64	0	1	31	4	...	...	...	...	...
			3/29	4:50 p.m.	19,800	56	0	0	36	8	43	0	1	48	8	...	...	...	...	...
2	9 mo.	Pertussis	20/21	7:30 p.m.	101,750	39	0	0	52	9						59	1	0	35	5
3	6 mo.	Optic atrophy	8/30	4:40 p.m.	9,400	32	4	0	59	5	23	3	0	68	6	23	1	0	70	6
			8/31	5:00 p.m.	13,200	36	1	0	53	10	24	0	0	71	5	23	1	0	71	5
4	5 mo.	Tuberculous meningitis; miliary tuberculosis	9/25	4:20 p.m.	19,600	52	0	0	30	18	56	0	0	36	8	52	0	0	40	8
5	10 mo.	Tuberculous meningitis; miliary tuberculosis	11/ 2	4:20 p.m.	16,500	58	0	0	29	13	33	0	0	36	31	32	0	0	31	37
			11/ 9	5:10 p.m.	11,300	49	1	0	19	31	44	0	0	19	37	44	1	0	17	37
6	5 wk.	Enlarged mediastinal shadow; negative tuberculin	9/11	4:45 p.m.	6,800	37	2	0	46	15	28	2	1	60	9	28	4	3	65	0
7	5 mo.	Enlarged mediastinal shadow; negative tuberculin	9/24	3:30 p.m.	11,600	56	3	0	29	12	43	2	0	50	5	36	2	0	56	5
8	8 mo.	Rickets; secondary anemia	6/14	4:45 p.m.	8,800	39	0	0	56	5	24	0	0	74	2	10	0	0	71	2
9	2 wk.	Severe anemia of new-born infants	2/27	1:25 p.m.	15,200	41	4	0	51	4	33	4	3	56	4	...	...	...	...	...
10*	9 mo.	Acute upper respiratory infection; tetany	5/ 8	4:45 p.m.	26,100	67	0	0	26	6	55	0	0	39	6	55	0	0	37	8
			5/25	12:10 p.m.	7,200	50	5	0	35	10	45	0	1	44	10	40	1	0	54	4
11	6 wk.	Bronchopneumonia	5/ 3	5:20 p.m.	11,300	71	1	0	19	9	57	0	0	34	9	...	...	...	...	...
			5/14	4:45 p.m.	20,300	73	0	0	25	2	80	0	0	16	4	73	0	0	20	7
12	4 mo.	Bronchopneumonia	2/27	2:00 p.m.	11,200	49	4	0	41	6	41	0	0	54	5	...	...	...	...	...
13	8½ mo.	Bronchopneumonia	1/30	5:00 p.m.	19,400	66	0	0	32	2	...	...	...	...	...	76	0	0	19	5
14†	11 mo.	Lobar pneumonia	6/28	3:30 p.m.	46,800	66	2	0	24	5	61	0	0	30	9	65	0	0	31	4
15‡	9 mo.	Empyema	7/ 6	5:10 p.m.	12,200	57	2	0	27	12	54	0	0	34	12	...	...	...	...	...
			7/24	4:20 p.m.	48,000	83	0	0	12	5	78	0	0	20	2	69	0	0	28	3
			9/ 6	5:10 p.m.	18,600	61	3	0	29	7	54	1	1	38	6	52	2	1	40	6
16	10 mo.	Empyema	8/14	4:40 p.m.	37,000	93	0	0	6	1	85	0	0	13	2	78	0	0	20	2
			10/ 3	5:05 p.m.	19,600	56	2	0	34	8	46	1	0	50	3	47	1	0	49	3

* One eosinocyte was present in the supravital preparation in the first observation. None were found in the fixed smears.

† Three eosinocytes were present in the supravital preparation in the first observation and two in the second. No eosinocytes were found in the fixed smears on either day.

‡ In the first observation two myelocytes were noted in the supravital preparation. No myelocytes were found in any of the fixed smears.

in an infant with empyema in whose blood the percentage of neutrophils was respectively 93, 85 and 78 in the supravital preparation, coverslip and slides with Wright's stain. On the other hand, in an infant with bronchopneumonia, case 11 (first count), table 2, the supravital differential count resulted in 71 per cent of polymorphonuclears as compared with 57 per cent of the fixed coverslip smear. Not knowing the actual polymorphonuclear percentage in the living preparation, the degree of resistance to infection by the patient would be called into consideration.

COMMENT

The results bear out the observations of Sabin, Cunningham, Doan and Kindwall[8] and of Rogers,[8] namely, that in fixed smears a lower polymorphonuclear leukocyte count is obtained than in the supravital preparations. The observations noted in the preceding tables emphasize the importance of discounting at times a high lymphocyte count in the differential count from the fixed smear. The discrepancies cited also hold for the blood of older children and adults, but they are of particular significance in the blood smears of the infant where the lymphocyte is the predominant cell. In new-born infants, too, Forkner[9] has pointed out the difficulties of identifying the distorted cells of the fixed smears and the more satisfactory results obtained from supravital examinations.

The differences in the counts by the two methods, the vital and the fixed, may be attributed to several causes. In each method there are possibilities for error inherent in the individual technic. With the supravital preparation, the dyes must be of a concentration sufficient to secure staining of the cytoplasmic structures, such as granules, vacuoles and mitochondria, without staining of the nucleus and without impairing the motility of the cells. If a stain has not been sufficiently diluted, or if traces of acid are left on the slide, diminished motility results, with staining of the nucleus and early degeneration of the cells. With rigid attention to technical details, injury to the cells becomes negligible. With a drop of blood that is not too thick, even distribution of the cells is entirely possible, as evidenced by the similarity of consecutive differential counts.

With the fixed smears, the sources of error are more numerous. A fixed blood film on a slide yields differential counts that vary widely, depending on what part of the slide is examined. Gyllensward[2] pointed out that the distribution of the cells in a single preparation may be so unequal that a relative lymphocytosis may be obtained from the middle

8. Rogers, P. M.: A Study of the Blood Monocytes in Children with Tuberculosis, New England J. Med. **198**:740 (May 24) 1928.

9. Forkner, C. A.: Studies on the Living Blood Cells of the Newborn, Bull. Johns Hopkins Hosp. **45**:75 (Aug.) 1929.

part of the smear and a neutrophilic leukocytosis from the edges. When the coverslip is used, this factor is not as significant.

With both fixed smear methods, the element of cell fragmentation plays an important rôle. There may be found on coverslip or slide such large numbers of traumatized white cells that an accurate differential count is impossible. This condition accounts in the main for the great disparity between the vital and the fixed smears when it occurs. A polymorphous nucleus alone or one with the telltale neutrophilic or eosinophilic granules in its vicinity can be identified. But even with the most minute care so as not to exert undue pressure in drawing the drops of blood across the slide or in pulling the coverslips apart, the resulting smears may contain a large number of amorphous masses of stained cytoplasm or chromatin to which the proper cytologic terminology cannot be applied.

In the presentation of studies involving series of differential counts, one sometimes finds the statement that these masses have been disregarded. It at once becomes apparent in comparing such fixed smears with the corresponding supravital preparation that the bulk of these smudges belongs to the group of polymorphonuclear leukocytes. I have found in pyogenic infections associated with a marked leukocytosis for which an increase in polymorphonuclear leukocytes is responsible that even with the most rigid attention to technic the fragility of white cells is most in evidence. With the vital stain, too, there is a tendency to early degeneration, but the identification of the cells is possible before the changes become too pronounced. Lewis and Shope [10] recently noted similar damage to the polymorphonuclear neutrophils and eosinophils in experimentally induced hog cholera. Disruption of these cells was so extreme that they did not appear at all in the fixed blood smears and were observed only in the supravital preparations.

The tendency for the fragmented and intact cells of the fixed smears to be crowded together in both normal and pathologic cases accounts, I believe, for those instances mentioned in which the polymorphonuclear leukocytes run higher in the fixed than in the supravital preparation.

The fragility of cells necessitates a discussion of the nonmotile cell. Sabin called attention to a type of polymorphonuclear leukocyte found in the living smears in which active ameboid motion is lost, the cell rounds up, the nucleus assumes an edematous appearance and large granules replace the fine neutrophilic granulation. When blood counts were taken at fifteen minute intervals, Sabin, Cunningham, Doan and Kindwall [8] found that the nonmotile or dying cells occur during the day in showers, and that following them there is a rise in the number of motile leuko-

10. Lewis, P. A., and Shope, R. E.: The Blood in Hog Cholera, J. Exper. Med. **50**: 719 (Dec.) 1929.

cytes. They conjecture from their data the possible relationship between the nonmotile cells and their subsequent replacement by living cells in the circulation and their fundamental importance in maintaining the normal white blood cell level. It may be conceived, they indicate, that these dying cells give off a substance which attracts freshly formed leukocytes from their reservoirs. In correlating their supravital differential counts with those from the fixed smears, they found that the fragile cells and free nuclei of the fixed film correspond in percentage approximately with the nonmotile leukocytes of the supravital preparation.

Smith and McDowell,[11] on the basis of studies similar to those of Sabin and her co-workers, conclude that the nonmotile cell is accidentally produced in the course of preparing the film. It is nevertheless true that when the essential care is exercised the nonmotile cell is found in the same field with active leukocytes, an observation which discredits the idea that its appearance is dependent solely on external conditions. In the present study, I found instances in which the number of dying cells in the supravital preparation had its approximate numerical counterpart in the disintegrating cells of the fixed smear. More often, however, a close correspondence did not exist. It was more common to find but an occasional nonmotile form among the living cells and a considerable number of fragmented forms in the fixed film. This observation does not, however, discount the physiologic importance of the nonmotile cell; since it occurs in showers only sporadically in the circulation, it may be overlooked in the casual smear taken in the course of the day. With the same technic, the fragility of the white cells in the fixed smear is not a constant observation in the blood of all normal infants examined at the same time of the day. It is therefore conceivable that when it does occur, the phenomenon is related to impending cell death in the peripheral circulation.

Allowing for the factor of unequal cell distribution, which is much less in evidence in the fixed smear of the coverslip than of the slide, the difference between the percentage of all polymorphonuclears, motile and nonmotile, in the supravital differential count and of the intact cells only in the fixed smear could very well serve as an index of white cell fragility. It seems apparent also that in reporting a routine differential white count from the fixed smear, a notation should be included as to the amount of cell fragmentation observed. This additional information would be of importance particularly in conditions in which the differential white count is employed in gaging the resistance of the patient to an acute infection.

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11. Smith, C., and McDowell, M. A.: Normal Rhythm of White Blood Cells in Women, Arch. Int. Med. **43**:68 (Jan.) 1929.

The cases in both tables show a slightly higher percentage for the eosinophils and monocytes in the supravital counts than in the fixed smears. The reason probably lies in the readier recognition of these cells in the living preparation. The increased numbers of eosinophilic leukocytes in normal cases, 10 and 21 (table 1), may be associated with the introduction of new food factors in the diet.

These studies further emphasize the advantage of the supravital over the fixed smear count in tuberculosis. Following the investigations of Sabin and her co-workers[12] on the monocyte in tuberculosis of the rabbit, the peripheral blood has been studied from this point of view in human cases. The monocyte to lymphocyte ratio determined from the differential count has been found to bear a significant relationship to the activity of the infection. A fixed smear presenting an exaggerated lymphocytic percentage would, of course, vitiate the reliability of this ratio (cases 4 and 5, table 2).

SUMMARY

The differential blood count of thirty-seven normal and sick infants was studied from a supravital preparation and from fixed smears, and the observations were correlated. In forty-three of forty-eight comparative smears, the percentage of polymorphonuclear leukocytes was higher, and that of lymphocytes was lower in the living preparation than in the fixed film.

The average of twenty-four counts from the group of normal infants showed the percentage of polymorphonuclear neutrophils to be 8.6 per cent higher in the supravital than in the fixed cover-slip smear and almost 12 per cent higher than in the slide. The lymphocytes, on the other hand, ran 14 per cent and 11 per cent higher in the fixed smear of the slide and coverslip, respectively, than the corresponding cells of the supravital preparation.

The principal reasons for this discrepancy are unequal distribution of the cells and, especially, failure to identify and include all fragmented polymorphonuclear leukocytes in the differential count of the fixed smear. With the supravital technic, the spread of cells is more even, trauma is reduced, and both motile and dying cells may be more readily identified.

The lymphocyte has always been regarded as the predominant cell in the blood of the infant. This observation has heretofore been based on differential counts employing the fixed smear with some modification of the Romanowski strain. While counts made from the supravital film confirm the preponderance of lymphocytes over polymorphonuclear

12. Cunningham, R. S.; Sabin, F. R.; Sugiyama, S., and Kindwall, J. A.: Role of the Monocyte in Tuberculosis, Bull. Johns Hopkins Hosp. **37**:231 (Oct.) 1925.

leukocytes, it is often by no means as marked as indicated in the fixed smear. The differential count from the fixed smear may unduly exaggerate the lymphocytic percentage and convey an erroneous impression of a blood dyscrasia.

In pyogenic infections, especially when associated with a leukocytosis, the differential count from the fixed smears gives at times a much lower polymorphonuclear and a higher lymphocyte percentage than expected. That this discrepancy is often due to an increased fragility of the polymorphonuclear leukocytes is evident from comparative supravital studies. In a routine differential count from the fixed smear, particularly when it is employed as an index of the patient's resistance, the extent of white cell damage encountered on the slide should be noted. If fragmented cells have been included in determining the individual cell percentages, mention of this fact should also be made.

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SEPSIS WITH LEUKOPENIA (AGRANULOCYTOSIS) IN CHILDREN

REPORT OF TEN CASES *

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Seven or eight years ago, an infant about 1 year of age entered the Children's Memorial Hospital showing the clinical picture of acute sepsis, with high fluctuating temperature, yellowish color, slightly enlarged spleen and a fairly abundant crop of petechiae. Immediately after admission, the child was presented at a postgraduate clinic by one of us (J. B.) as having severe sepsis of unknown origin. The blood count, however, revealed marked anemia and still more marked leukopenia, with an almost complete absence of polymorphonuclear cells. The diagnosis was changed to that of an aleukemic stage of acute lymphatic leukemia, and the case, as was expected, went on to a rapidly fatal termination, with an ever-increasing exacerbation of all the cardinal symptoms. The history of this case, unfortunately, cannot be found, and so the exact details are not reportable. It made, however, a deep impression, as we had never encountered the much discussed aleukemia, except in the course of an evident leukemia, and then never with so great a degree of leukopenia.

Since then, nine more children have entered the hospital, each with a clinical picture and rapidly fatal course so similar to, not to say identical with, the first that we could almost recognize their condition at a glance, without a knowledge of the blood picture. With a knowledge of the blood picture, the characteristic leukopenia, we could predict with certainty the approximate time at which death would occur. In all of them there was left no doubt with the appearance of the cardinal symptoms: septic temperature, anemia, marked, steadily increasing leukopenia (in several cases, as low as 800 or 900 white cells) and always a decrease of the polymorphonuclear cells to less than 12 per cent, often to 1 or 2 per cent. In only one of them was there at any time a white blood count above normal. In the earlier cases, the record of our examinations of the blood leaves much to be desired. In all of the later cases there was marked thrombopenia. Only three

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autopsies were obtained. In spite of these defects in the records, the clinical similarity of all of these cases leaves no doubt in our minds that they all belong in the same category. That there is an aplastic picture is evident, but that they do not fit fully into the commonly accepted rare picture of aplastic anemia is also evident. A search of the literature leaves us still in doubt as to their proper position in that large group of severe anemias in children in which leukopenia is so pronounced. It is our purpose to report these cases as an interesting group, clinically identical, in which there is a failure of regeneration of the bone-marrow cells, apparently due to the effect of a septic infection or toxic reaction of the bone-marrow.

The following report of cases and postmortem observations is made as brief as possible by including only the essential data. So far as possible, all cases thought to be cases of leukemia in the aleukemic phase were excluded.

REPORT OF CASES

CASE 1.—*History.*—A. M. E., a white girl, aged 7, entered the hospital on April 4, 1928, to have her tonsils and adenoids removed. There was a history of frequent infection of the upper part of the respiratory tract and periods of unaccountable fever which would last for several days. Two months previously, she had had pains in the left hip which lasted two weeks, and which had not been accompanied by swelling or discoloration. In the past history, the following diseases were noted: measles, chickenpox, pertussis and mumps, occurring several years before. The family history was negative.

Physical Examination.—The patient was well nourished and rather pale and did not appear ill. The tonsils were large and ragged. There was moderate cervical adenopathy. Otherwise, the results of physical examination were negative.

Laboratory Examination.—Bleeding time and clotting time were normal. The urine was normal. The result of the Pirquet test was negative. A throat culture was negative for Klebs Löffler bacilli.

Course.—The patient's temperature (rectal) on admission was 99.4 F. After the tonsils and adenoids had been removed, on the day of admission, the temperature rose to 103 F. and remained there for four days, and then gradually returned to normal. There was no postoperative hemorrhage, but a large gray sloughing area appeared on the pharynx and in the tonsillar beds. The patient was discharged on April 12, in apparently good condition.

April 17: The patient returned to the outpatient department after spitting up a small blood clot. There was a small blood clot in the right tonsillar fossa, but no evidence of bleeding at this time.

May 29: The patient was again admitted to the hospital. During the past month, she had had pains in the shoulders, left wrist and left hip, but no swelling or discoloration. She had been having fever and had been in bed for the previous three weeks.

Physical Examination on Second Admission.—The patient was well nourished. She was acutely ill and apparently in pain. The skin was pale and lemon yellow. The mucous membranes were pale. The mouth showed dental caries; the tonsils were out; no oral hemorrhages or ulcerations were present. The lungs were

normal. The borders of the heart were within normal limits. At the apex, there was a soft systolic murmur which was not transmitted. The liver and the spleen were not palpable. The reflexes of the extremities were normal. The left wrist and thumb and the joints of both hands were painful, but not swollen or discolored.

Course Following Second Admission.—The temperature was septic, rising to 106 F. toward the end. Several more joints became painful, but at no time was there any swelling or discoloration. The spleen became palpable 3 cm. below the costal margin, but gradually decreased in size so that it was just palpable. The cervical, axillary and inguinal lymph nodes became moderately palpable. During the last two weeks, petechiae appeared in the skin of the face, trunk and extremities. They were from red to bluish purple and faded to greenish yellow, varying in size from that of a pinhead to 1 cm. in diameter. During the last week there was almost continuous oozing of blood from the nostrils, and a hemorrhagic

TABLE 1.—*Blood Counts of A. M. E., Case 1*

Date	Hemoglobin, per Cent	Red Cells	White Cells	Polymorphonuclear Neutrophils	Lymphocytes† Total	Lymphocytes† Large	Lymphocytes† Small	Large Mononuclears	Bleeding Time	Platelets
6/29	50	1,620,000	8,100	2	97	...	..	1	.....	.....
6/ 8	50	1,750,000	8,300	7	89	...	..	4	.....	.....
6/17	50	1,664,000	5,800	1	98	8	90	1	.....	.....
6/18	Blood transfusion									
6/19	55	1,900,000	4,600	9	88	...	..	...	.....	.....
6/26	Blood transfusion			...	..	...	..	.	2¾ hr.	.....
6/27	55	1,710,000	3,100	7	92	...	..	1	21 min.	.....
6/28	50	1,630,000	2,400	6	93	...	..	1	3½ hr.	42,000
6/30	58	1,900,000	2,425	4	96	...	..	...	3½ hr.	40,000
7/1	Blood transfusion									
7/3	50	1,580,000	2,550	2	96	6	90	2	.....	5,000
	Vital stain: no granular cells									
7/5	50	1,450,000	2,300	...	...	...	..	...	10½ hr.	.....

No nucleated red cells were seen. Slight anisocytosis, poikilocytosis and achromia were noted.

† The lymphocytes appeared to be normal.

swelling developed about the left eye. The results of the Wassermann and Kahn tests of the blood were negative, as was that of the Pirquet test. The urine was essentially normal. On five repeated cultures of the blood, there was a pure growth of *Staphylococcus albus*. The systolic blood pressure was 84, and the diastolic, 62. The result of the fragility test of the red blood cells on July 5 was from 0.36 to 0.4. The patient died five weeks after admission to the hospital and about five months after the onset of symptoms.

Necropsy.—The postmortem examination was made by Dr. W. G. Hibbs and one of us (J. A. B.). The body was that of a well developed but undernourished child. The skin was pale with a yellow tint and contained many petechiae. The fat was bright yellow.

The peritoneum was smooth and shiny. There was no free fluid in the peritoneal cavity. Petechial hemorrhages were observed in the peritoneum, mesentery, urinary bladder, esophagus, bowel and stomach.

The spleen weighed 90 Gm. and measured 10 by 6 by 3.5 cm. It was soft and dark purplish red. On cut sections, the surfaces exuded blood, and the malpighian corpuscles were small and fairly distinct. On microscopic examination, the mal-

pighian corpuscles were large and appeared normal. Some of the blood vessels were plugged with emboli. Hemosiderin was present. No early cell forms were seen.

The liver weighed 705 Gm., was firm and reddish brown and had a smooth capsule. On cut sections, the surfaces were light brown, with indistinct lobulations. Microscopic examination revealed evidence of phagocytosis by the Kupffer cells, slight fatty changes, large deposits of hemosiderin, and in the sinusoids a few mononuclear cells.

The kidneys were alike and together weighed 245 Gm., and measured 11 by 5.5 by 3 cm. They were firm, and the capsules stripped easily, leaving a smooth pale surface that contained a few small petechial hemorrhages. On cut sections, the edges everted, and the cut surfaces had a pale yellow appearance, with indistinct glomeruli and striations.

Microscopically, the cells of the convoluted tubules were seen to be swollen and to contain granules. There was a small amount of round cell infiltration in the interstitial tissue. There were emboli in the small arterioles.

In each pleural cavity, there was 40 cc. of clear yellow fluid. There were many petechial hemorrhages in the visceral pleurae. Scattered over the pleurae were a few miliary abscesses, from 2 to 8 mm. in diameter, with yellow centers and hyperemic peripheries, which extended into the pulmonary tissue. There was no gross evidence of consolidation. Microscopically, the alveoli and interstitial tissue showed no change, except for small abscesses with necrotic centers surrounded by round cells, red cells and a few polymorphonuclears. There was no evidence of tuberculosis.

In the visceral pericardium and in the myocardium, there were small petechial hemorrhages. The heart valves were normal. Microscopically, the small arterioles contained emboli. In the heart muscle there was beginning fibrous change and round cell infiltration.

The thymus, suprarenal glands and the pancreas were within normal limits.

The lymph nodes all showed slight hyperplasia. Two of the cecal lymph nodes contained calcium. Microscopically, the lymph nodes showed relatively the same changes as in the spleen.

The bone-marrow of the ribs, sternum and femur contained no fatty areas, but was pink and jelly-like. Microscopically, it presented no islands of blood forming tissue. There was a total absence of polymorphonuclears, myelocytes, nucleated red cells, megaloblasts and megalokaryocytes. The surviving cells were large mononuclears with agranular cytoplasm. It is safest to consider these as reticuloendothelial cells or macrophages. They were 15 microns in diameter, and some of them contained a foamy, vacuolated cytoplasm. The nuclei were undergoing division, and in some cells two definite nuclei could be seen. In some cells pyknotic nuclei were present. These cells were the remains of polymorphonuclears. Oxidase stains were negative for cells of the granular series.

In cultures of the bone-marrow, blood, spleen, pleural fluid and the lung abscesses there was a pure growth of *Staphylococcus albus*.

Case 2.—*History.*—E. L., a white girl, aged 6, entered the hospital on July 8, 1924. Two months previously, she had become less active than normally, and the appetite became poor. She had been confined to bed for the past four weeks with irregular fever as high as 101 F., progressive weakness and paleness. There had been no rash present. In the past history, measles and varicella were noted. Five weeks before admission, she had had "serum" injections at school. There had been occasional attacks of tonsillitis. The family history was negative.

Physical Examination.—The child was well nourished, but extremely weak. The mucous membranes and skin were pale. There were several petechial hemorrhages on the legs with ecchymosis about the ankles. The tonsils were enlarged, with hemorrhagic areas in crypts. The lungs were not abnormal. At the apex of the heart, a loud systolic murmur was heard, slightly transmitted toward the left axilla. The left border of the heart was 2 cm. outside of the left nipple line.

The edge of the liver was firm and was felt 2½ fingerbreadths below the costal margin. The spleen was palpable 4 cm. below the costal margin and was tender.

The cervical, epitrochlear and inguinal lymph nodes displayed moderate adenopathy.

Course of Illness.—There was progressive weakness, with fever from 102 to 105 F. There was indefinite tenderness over the long bones. The heart did not increase in size, but the murmur became musical and inconstant. Petechial hemorrhages became numerous and generalized. Ulcerations appeared about the gums five days before death, with painful swelling of the cervical lymph nodes. The spleen decreased in size so that three days before death it was no longer palpable.

TABLE 2.—*Blood Counts of E. L., Case 2*

Date	Hemoglobin, per Cent	Red Cells	White Cells	Polymorphonuclear Neutrophils	Lymphocytes†			Large Mononuclears	Eosinophils
					Total	Large	Small		
7/8	10	1,020,000	41,000	..	..	..	..	..	..
7/8	Blood transfusion								
7/9	28	2,220,000	10,200	4	95	75	20	1	..
7/13	26	1,520,000	4,200	1	93	82	11	6	..
7/15	20	.....	3,100	1	89	60	29	10	..
7/18	17	1,110,000	2,050	4	91	66	25	5	..
7/19	16	1,100,000	2,010	1	97	12	85	0	2

Slight anisocytosis, poikilocytosis and polychromasia were noted. Nucleated red cells were not noted.

† The lymphocytes appeared to be normal.

There was troublesome oozing of blood from incisions over veins. The result of the Wassermann test of the blood was negative, and the urine was normal. Blood cultured on July 9 yielded no growth. On July 19, blood cultured in broth yielded no growth, but on blood agar there grew some isolated gray colonies that were gram-positive cocci of the *Staphylococcus* group, type undetermined. These organisms resembled cocci seen in a blood smear, July 18. Death occurred fifteen days after admission and ten weeks after the onset of symptoms.

Necropsy.—The postmortem examination was made by Dr. W. G. Hibbs. The anatomic diagnosis was: marked generalized anemia; multiple petechial hemorrhages in the skin, pleurae, pericardium, dome of the liver and lining of the stomach; hyperplasia of the mesenteric, peribiliary, peripancreatic, peribronchial and peritracheal lymph nodes; hyperplasia of the spleen; brown pigmentation of the kidneys, liver, myocardium and suprarenal cortices; slight fatty changes of the liver, and hypostatic hyperemia and edema of the right lung. The bone-marrow was red, but unfortunately slides were not made of it.

CASE 3.—*History.*—G. F., a white girl, aged 11, was admitted to the hospital on Oct. 24, 1922. About July 1, she had had an acute onset of symptoms with a cold, fever and pains in the knees, hips and spine that confined her to bed for one week. At this time, pallor had become evident. There had been progressive weak-

ness. The patient had been in bed a good share of the time since the onset. There had been no swelling or discoloration of the joints. The temperature since the onset had always been over 100 F. There had been frequent vomiting after eating and some dyspnea during the past two weeks. The tonsils and adenoids had been removed in 1919; the patient had had influenza in 1919 and she had had some pain in the shoulder joints in March, 1922, which had lasted only a short time. The family history was negative.

Physical Examination.—Physical examination showed a well nourished, acutely ill Jewish child. The skin had a yellow color and was pale, as were the mucous membranes. Examination of the mouth showed nothing abnormal. The lungs were normal. At the apex of the heart there was a soft systolic murmur which was not transmitted. The borders of the heart were within normal limits. The liver and the spleen were not palpable. Examination of the extremities revealed no pain, tenderness, swelling or discoloration of the joints at this time. Moderate lymphadenopathy of the cervical region was noted.

TABLE 3.—*Blood Counts of G. F., Case 3*

Date	Hemoglobin, Per Cent	Red Cells	White Cells	Polymorphonuclear Neutrophils	Lymphocytes* Total	Lymphocytes* Large	Lymphocytes* Small	Large Mononuclear Myelocytes	Nucleated Red Cells
10/30	40	1,840,000	4,000	41	50	4	55	5	1
11/11	30	1,560,000	6,400	10	84	16	68	6	
11/14	40	1,680,000	6,000	5	90	37	53	5	
11/16	50	1,960,000	4,800	6	87	10	87	7	
11/20	30	1,480,000	5,400	6	85	14	80	4	
11/28	0	1,040,000	3,000	6	94	20	74	1	
12/ 2	0	870,000	6,400	1	99	99	99	5	
12/ 3	Blood transfusion								
12/ 5	30	1,040,000	7,100	6	93	17	76	5	
12/12	Blood transfusion								
12/15	40	5,240,000	1,900	3	97	16	81	5	
12/17	30	1,040,000	850	..	..	..	..	..	
12/20	0	940,000	850	..	..	..	..	..	

Moderate anisocytosis and poikilocytosis were observed.
* The lymphocytes appeared to be normal.

Course of Illness.—The patient showed increasing pallor, weakness and dyspnea with the temperature hovering around 101 F. at first and then increasing to 103. Two weeks after admission, the spleen began to enlarge and was palpable 6 cm. below the costal margin. It was firm, and in the course of the next few weeks it decreased in size so that before death it was just palpable. The axillary, epitrochlear and inguinal lymph nodes became slightly enlarged. Four weeks after admission, petechial hemorrhages appeared in the skin. Toward the end there were troublesome nosebleeds. During the last week, bronchopneumonia developed. The blood pressure was 104 systolic and 85 diastolic. The urine at first contained albumin and casts, but later became normal. The result of the Widal test was negative. Cultures of the blood on several occasions yielded no growth. Death occurred two months after admission and five and a half months after the onset of symptoms.

CASE 4.—*History.*—R. J., a white boy, aged 5, was admitted to the hospital on June 29, 1927. Six weeks previously, he had suffered an acute onset of pain in the legs and elbows, without swelling or discoloration. Also he had had some generalized pains in the abdomen. Four weeks previously, he began to get pale

and two weeks previously black and blue spots had appeared on the body. The general health had always been good, with the exception of chickenpox several years ago. The family history was negative.

Physical Examination.—The child was well nourished and acutely ill. The skin was pale with a yellow color and contained numerous petechial hemorrhages. The mucous membranes were pale. The tonsils were large. The lungs were normal. The borders of the heart were within normal limits. At the apex there was a soft systolic murmur which was not transmitted to the left. The spleen was firm and palpable 4 fingerbreadths below the costal margin. The edge of the liver was firm, smooth and palpable 3 fingerbreadths below the costal margin. There was a rather marked lymphadenopathy in the neck.

Course.—The temperature of the patient was septic, varying between 100 and 105 F. Pallor increased, and new crops of petechiae appeared. The liver and the spleen decreased in size so that the spleen reached only 1 fingerbreadth, and the liver, 2 fingerbreadths, below the costal margins. The urine was normal. Death occured eleven days after the patient entered the hospital and eight weeks after the onset of symptoms.

TABLE 4.—*Blood Counts of R. J., Case 4*

Date	Hemoglobin, Grams per Cent	Red Cells	White Cells	Polymorphonuclear Neutrophils	Lymphocytes† Total	Lymphocytes† Large	Lymphocytes† Small	Large Mononuclears	Platelets	Bleeding Time
6/30	38	2,000,000	10,000	8	87	13	79	4	40,000	Increased
6/30	30	2,048,000	12,000	13	83	19	68	4	.....	Increased
6/30	Blood transfusion									
7/1	38	2,250,000	6,400	7	89	61	33	4	33,000	Increased
7/2	36	2,180,000	4,000	6	86	33	64	8	.....	Increased

Moderate anisocytosis, poikilocytosis and achromasia were noted. No nucleated red cells were seen.

† The lymphocytes appeared to be normal.

CASE 5.—*History.*—A. J., a white boy, aged 2, was admitted to the hospital on Dec. 23, 1925. Two months previously, he had begun to have loss of appetite, and three weeks previously, progressive weakness, so that at the time of admission to the hospital he could not stand alone. Ten days previously there had been vomiting that lasted two days, and since then, increasing pallor. During the previous three days, there had been some fever and some black and blue spots on the body. The child had always been healthy. The family history indicated that the father had pulmonary tuberculosis; otherwise, the family history was negative.

Physical Examination.—The child was well nourished and acutely ill. The skin and the mucous membranes were pale. There were several small brownish-yellow discolorations of the skin; these resembled old hemorrhages. The breath had a foul odor. The throat showed injection, and the tonsils were large, but there was no evidence of hemorrhages or ulcerations. The lungs appeared normal. At the apex of the heart, there was a soft systolic murmur, which was not transmitted to the left. The borders of the heart were within normal limits. The edge of the liver was just palpable. The spleen was not palpable. There was a slight pitting edema of the hands and legs. The cervical, axillary and inguinal lymph nodes were moderately enlarged.

Course.—The temperature was septic, varying between 103 and 106 F. daily. A few petechial hemorrhages developed on the second day after admission. The

urine was normal. The result of the Widal test was negative. Cultures of the blood yielded no growth. Death occurred six days after admission and nine weeks after the onset of symptoms.

CASE 6.—*History.*—J. M., an Italian boy, aged 3½, was admitted to the hospital on Jan. 30, 1925. He had been well up to two months before. Then there had been a marked decrease in his activity. For six weeks previous to admission there had been increasing pallor, listlessness, irritability and some loss in weight. The mother thought that there had been some fever. He had always been healthy. The family history was negative.

Physical Examination.—The child was fairly well nourished and acutely ill. The skin was waxy pale, with small petechial hemorrhages in it. The mucous membranes were pale. The pharynx was moderately red, and the tonsils were

TABLE 5.—*Blood Counts of A. J., Case 5*

Date	Hemoglobin, per Cent	Red Cells	White Cells	Polymorphonuclear Neutrophils	Lymphocytes†			Large Mononuclears
					Total	Large	Small	
12/24	40	1,480,000	1,800	4	92	14	78	4
12/25	40	1,640,000	1,690	0	100	2	98	0
	Oxidase stain; no granular cells							
12/28	40	1,580,000	2,100	0	100	0	100	0

Slight anisocytosis and poikilocytosis were noted. No nucleated red cells were seen.
† The lymphocytes appeared to be normal.

TABLE 6.—*Blood Counts of J. M., Case 6*

Date	Hemoglobin, per Cent	Red Cells	White Cells	Polymorphonuclear Neutrophils	Lymphocytes†			Platelets	Bleeding Time	Clotting Time
					Total	Large	Small			
1/30	55	2,800,000	2,500	7	93	10	83	Decreased	2-4 hr.	2 min.
2/2	...	.....	1,500	12	88	5	83	Decreased		
2/2	Blood transfusion									
2/3	45	2,200,000	895	6	94	10	84	Decreased		

No nucleated red cells were noted.
† No changes were noted in the lymphocytes.

large. There were no ulcerations or hemorrhages. The lungs appeared normal. At the apex of the heart, a soft systolic murmur was heard, which was transmitted only slightly to the left. The borders of the heart were within normal limits. The liver and the spleen were not palpable. The cervical, epitrochlear and inguinal lymph nodes were moderately enlarged.

Course.—The temperature varied between 101 and 106 F. daily. New petechial hemorrhages appeared in the skin, and there developed troublesome bleeding from the gums, lips and from an incision over a vein. The urine was normal. The results of the Pirquet test, the Wassermann and Kahn tests of the blood and the Widal test were negative. Death occurred on the fifth day after admission and nine weeks after the onset of symptoms.

CASE 7.—*History.*—M. K., a white girl, aged 6, was admitted to the hospital on Nov. 11, 1928. Three days before, she had had an acute onset of what seemed to be an infection of the upper part of the respiratory tract, with fever, sore

throat and vomiting. Her previous health had been good. At 2 years of age, she had had a congenital deformity of the hip repaired. The family history was negative.

Physical Examination.—Physical examination showed a well nourished, feverish, acutely ill, rather pale child. The throat was injected; the tonsils were large and cryptic. There was moderate cervical adenopathy. The heart and the lungs were normal. The liver and the spleen were not palpable.

Course.—The patient looked ill out of proportion to the physical observations. Three days after admission, the liver became palpable 2 cm. below the costal margin. The temperature varied around 104 F. the first five days and then gradually came down to normal. The urine was normal. The result of the Pirquet test was negative. The child looked much improved, and when she was discharged, ten days after admission, the symptoms had disappeared.

The patient was readmitted to the hospital on March 15, 1929. She had seemed to be well to one month before, when it was noticed that she was becoming pale. Two weeks later she had become acutely ill, with sore throat, fever, vom-

TABLE 7.—*Blood Counts of M. K., Case 7*

Date	Hemoglobin, per Cent	Red Cells	White Cells	Polymorphonuclear Neutrophils	Lymphocytes† Total	Lymphocytes† Large	Lymphocytes† Small	Large Mononuclears	Unidentified	Myelocytes	Platelets
11/12	40	4,060,000	4,700	21	76	23	53	1	2	..	..
11/13	..	.....	6,150	18	76	8	68	4	0	..	..
				Second Admission							
3/15	35	1,096,000	1,200	12	86	6	80	0	0	2	60,000

With oxidase stain, a few myelocytes and lymphoblasts were seen.

Moderate anisocytosis, poikilocytosis and achromasia were observed. No nucleated red cells were seen.

† The lymphocytes appeared to be normal.

iting and pains in her legs and arms, but without swelling or discoloration of the joints. Since then weakness had become marked, and there was some pain in the abdomen. The day before admission black and blue spots had been noticed on the arms and legs.

Physical Examination.—Physical examination showed a well nourished, acutely ill child. The skin was pale and yellowish and contained many petechial hemorrhages. The mucous membranes were pale. The pharynx was injected. The tonsils were cryptic, but not large. The lungs were normal. At the apex of the heart, a soft systolic murmur was present, which was not transmitted to the left. The borders of the heart were within normal limits. The spleen was not palpable. The edge of the liver was palpable 2 fingerbreadths below the costal margin. The legs were painful to touch and motion. There was no swelling or discoloration. There were a few isolated palpable cervical lymph nodes.

Course.—The temperature varied between 103 and 106 F. On the day of death, the left border of the heart was found 4 cm. to the left of the nipple line, but there was no change in the soft systolic murmur. This sudden enlargement occurred within twenty-four hours. Cultures of the blood yielded no growth. Death occurred two days after admission and five months after the onset.

Case 8.—*History.*—L. G., a white girl, aged 3½, was admitted to the hospital on Aug. 12, 1924. There had been frequent urination, fever, chills and sweats and loss of appetite for six days. Unfortunately, no other history was obtainable as to the present condition. In the past history were frequent bronchitis, measles and pertussis. The family history was negative.

Physical Examination.—The child was well nourished and acutely ill. The skin and mucous membranes were pale. The tonsils were extremely large and showed injection but no ulcerations. The lungs were normal. The heart was normal. The liver and the spleen were just palpable below the costal margins. There was moderate lymphadenopathy of the cervical, epitrochlear, axillary and inguinal nodes.

Course.—The temperature varied between 101 and 103 F. Two days after admission, purpuric spots appeared on the extremities, and there was a hemorrhagic area about one ear. At no time were there any cardiac abnormalities. The spleen did not increase in size, nor did the lymph nodes. The urine the first few days contained albumin and many leukocytes, but when the patient was discharged, there was only a trace of albumin. The Wassermann reaction of the blood was

Table 8.—*Blood Counts of L. G., Case 8*

Date	Hemoglobin, per Cent	Red Cells	White Cells	Polymorphonuclear Neutrophils	Lymphocytes			Large Mononuclears	Basophils	Bleeding Time and Clotting Time
					Total	Large	Small			
8/13	80	3,480,000	1,750	9	84	..	..	6	1	Increased
8/14	93	3,320,000	4,000	8	83	79	9	4	0	Increased
8/15	Blood transfusion									
8/17	94	3,300,000	2,550	7	80	81	9	3	0	Increased

No nucleated red cells were seen. Moderate anisocytosis and poikilocytosis were seen.
† The lymphocytes appeared to be normal.

negative. Cultures of the blood gave negative results. One week after admission, the patient was taken home against advice, with no improvement other than in the urinary condition, and she died seven weeks later.

Case 9.—*History.*—F. S., a white boy, aged 3½ years, entered the Children's Memorial Hospital on July 1, 1930. He had not been well since having pertussis eleven months before admission. Four months later, pain developed in the right ear, which began to drain spontaneously. During the three weeks before admission the discharge had been more profuse, and there had been earache and headache. Irritability and loss of appetite had been present. Pallor was noted about four months before admission, and swelling of the glands of the neck began three months before. Three weeks before coming to the hospital he fell downstairs, and he had nosebleed twice daily for the next three or four days. At this time he had a boil on his right heel, and since then there had been some pain in the right foot. For the past two weeks there had been continuous fever which was always higher at night. The past history was negative, except for chickenpox one year before admission. The family history was negative.

Physical Examination.—The child was fairly well nourished. He had a waxy, pale skin. On the right arm, there was a discoloration resembling an old bruise, which had been present for one week, and which had occurred spontaneously. The eyes were normal. The left ear was normal; the drum membrane of the right ear was dull, and there was no discharge at this time; there were, however,

some excoriations of the external auditory canal. The mouth was normal, except for large, spongy tonsils. There was a bilateral swelling of the cervical lymph nodes, which were larger on the right side. The heart was normal, except for a blowing systolic murmur at the base. The results of the examination of the lungs were within normal limits. The abdomen was normal. The liver and spleen were not palpable. The genitalia were normal. The extremities were normal, except for a healing pustular lesion on the right heel. The results of an examination of the nervous system were negative.

Course.—The temperature was of a septic nature, varying generally between 100 and 103 F. daily. Two days after admission a few small petechiae appeared on the right knee; later they appeared in the left groin, on the left leg and on the upper lip. Hemorrhages were also found in both the right and the left retinas. Severe pains developed in the arms and feet, and the legs became painful and tender. Before death there was edema of the face, scrotum and feet. The course was steadily down hill, except for a period of two days, four days after admission, when there was evidence of improvement. At that time

TABLE 9.—*Blood Count of F. Su, Case 9*

Date	Hemoglobin, per Cent	Red Cells	White Cells	Polymorphonuclear Neutrophils	Lymphocytes			Large Mononuclears	Eosinophils	Platelets
					Total	Large	Small			
7/3	37	3,140,000	5,500	0	93	..	..	3	..	60,000
7/5	..	.....	4,400	2	80	..	..	8		
7/7	30	.....	4,350	0	93	0	90	5	2	
7/8	..	.....	3,850	2	80	9	71	15	Vital stain	
7/10	10	1,500,000	3,300	6	88	0	88	6		
	Blood transfusion									
7/12	18	1,680,000	2,450							
7/13	..	.....	1,300	4	94	0	94	2		
7/15	..	1,400,000	1,450	...	79	12	67	16	Myelocytes 4 Megakaryocyte 1	

No nucleated red cells were seen. Moderate anisocytosis and poikilocytosis

the following note was made: "This child has a profound anemia, general sepsis, leukocyte count that has gone down from 9,000 to 4,500 within a few days, with 98 per cent leukocytes and with no evidence of enlargement of the liver and spleen. I do not believe this is a lymphatic leukemia, but it is one of those cases of aspesis with agranulocytosis. If it is, the leukocyte count will come down even lower, and there will be a fatal termination within a month or so." The urine was always normal. The Pirquet and Wassermann and Kahn tests of the blood were negative. The culture of the blood was negative. The fragility test of the red blood cells began at 0.4 and was complete at 0.32. No ulcerations appeared in the mouth, and the liver and spleen were never palpable. Death occurred seventeen days after admission to the hospital.

Necropsy.—The examination was made by Dr. W. G. Hibbs. The anatomic diagnosis was: marked generalized anemia; recent serofibrinopurulent pericarditis and myocarditis (*Staphylococcus aureus*); sero-sanguineous pleuritis, bilateral (*Staphylococcus aureus*); septicemia (*Staphylococcus aureus*); diffuse focal hemorrhages and focal edema of the lungs; hyperplasia of the spleen, of the peribronchial, periaortic, peribiliary and mesenteric lymph nodes and of the solitary and conglomerate lymphoid tissue of the lining of the bowel; extensive petechial hemorrhages into the lining of the renal pelves, ureters, stomach and

the lining of the colon; diffuse focal acute hepatitis; edema of the lining of the colon; diffuse focal hemorrhages of the kidneys; marked cloudy swelling of the myocardium, liver, pancreas and kidneys; fatty changes of the myocardium; irregular yellow material of the suprarenal cortices; moderate emaciation; serosanguineous ascites; diffuse fatty changes of the liver and kidneys; fragmentation of the myocardium.

The bone-marrow of the ribs and sternum was profoundly dark red; nowhere was it bright pink. There was no evidence of replacement with fatty marrow.

Wet smears stained with hematoxylin and eosin azure showed a definitely cellular structure, with a striking reduction in the number of granular cells, only an occasional myelocyte being present. A large number of large nongranular cells—with rather deeply stained chromatic network and clear slightly basophilic cytoplasm—which were interpreted as hemocytoblasts, were present. There was a very large number of small lymphocytes, and some erythroblasts and normoblasts with mitotic figures were present.

SUMMARY

In summarizing these cases it is seen that they have, strikingly, the same characteristics; gradual onset, fairly short course with fatal termination, fever, severe anemia, petechial hemorrhages with a low platelet count and leukopenia with a decrease in granulocytic cells.

Age and Sex.—The children ranged in age from 2 to 11 years. There were four boys and five girls.

Etiology.—Only in cases 1, 2 and 9 was anything found that might be considered an etiologic factor. In these, the blood cultures were positive for staphylococci. In case 2, the organisms were obtained in only one culture of the blood. In case 1, they were obtained during life in repeated cultures of the blood and at necropsy from the blood, spleen and bone marrow. In this case, one might question whether the organisms were present in the blood stream at the onset of the symptoms or whether they gained entrance at the time of the tonsillectomy, which took place two and a half months after the onset of the illness, according to the history. Immediately after the tonsils were removed, there was a period of high fever, and a large sloughing area appeared in the throat. The miliary abscesses in the lungs were of recent formation, and there was no evidence of old ones. The results of repeated cultures of the blood in all the other cases, except case 4 in which cultures were not taken, were negative. In practically all of the children there had been frequent sore throats, and in a few the onset of symptoms followed an infection of the throat. Unfortunately, no blood counts were performed earlier than five weeks before death.

Course.—In none of the cases was the onset acute, but in three there seemed to be some connection between the onset of symptoms and an acute infection of the upper part of the respiratory tract. In case 7 only did a physician see the patient early in the illness. In this case,

the patient had what appeared to be an acute infection of the upper part of the respiratory tract of only three days' duration and, as shown by examination of the blood, moderate anemia and moderate leukopenia in spite of a high fever and an illness out of all proportion to the physical observations. In the majority of cases, the onset was gradual, with loss of appetite, weakness, pallor, pain in the joints, etc. There was always a gradual increase in the severity of the symptoms, with periods during which the patient was confined to bed for several days at a time. Pallor was usually noted rather late, but this may have been due to lack of observation on the part of the parents. It is striking that all the children were well nourished. Fever to some degree was usually present, and while the patients were under observation it was always high and septic. As the anemia became more pronounced, prostration increased. Joint pains were present in six cases, but at no time was there redness, swelling or discoloration. Only in case 2 was there any tenderness over the long bones, and in this case it was rather indefinite. In one, there seemed to be some indefinite tenderness of muscle, but there never were any changes that could be interpreted as being due to hemorrhages in the deeper tissues or under the periosteum.

In four cases there was a lemon-yellow color of the skin, but never of the conjunctivae or mucous membranes. Petechial hemorrhages were present in all cases, occurring late, in one only as early as four weeks before death. These hemorrhages in the skin were small, and there were no extensive hemorrhagic areas. In about half the cases there was troublesome bleeding from the nose or lips or about the teeth; this bleeding always occurred late. There was prolonged bleeding from the site of puncture wounds for blood counts, etc. In no instance was there urinary bleeding or bleeding from the rectum. Bloody vomitus, when present, occurred as a terminal symptom only. At times, the stools gave a positive benzidine reaction for blood, but gross blood was never found.

Necrotic lesions in the mouth, in the skin or about the rectum were never present, except in case 1, as previously noted. In case 2, three weeks before death, small hemorrhagic areas were present in the crypts of the tonsils, and five days before death gingivitis and ulcerations about the teeth developed, accompanied by a painful swelling of the cervical lymph nodes draining these areas.

In all cases, except one, there was a soft systolic murmur present at the apex of the heart, but only in case 2 was there any evidence of its transmission to the left. In the latter instance there also was a slight enlargement of the heart to the left, the normal cardiac borders being present in all of the others. The murmurs were always considered to be functional. In the three necropsies, the cardiac valves were normal.

The liver was palpable and moderately enlarged in six patients at the time of their admission to the hospital and in none of them was there any further increase in hepatic size, but usually a gradual decrease. The spleen became moderately palpable only in five cases, and in all of these it decreased in size so that it could not be palpated, or remained only slightly enlarged. There was always a moderate enlargement of the cervical lymph nodes and frequency of the epitrochlear, axillary and inguinal nodes, as well.

The length of illness before death occurred as far as could be determined from the indefinite onset of symptoms, was five months in four cases and about two months in four cases. It is interesting that the duration of illness was longest in the older children.

Blood.—There was always severe anemia, with a reduction of the red cells in one child as low as 870,000 and with a decrease of the hemoglobin invariably below 30 per cent. A moderate anisocytosis and poikilocytosis, with some achromasia, were the rule. No nucleated red cells or megaloblasts were found, which points to an almost complete loss of the regenerative powers of the blood-forming organs.

Platelet counts were made in only six cases, in all of which there was a marked reduction, even as low as 4,000. When platelet counts were not made, it was noted in the course of the red cell counts and differential counts that much fewer platelets than normal were seen. The bleeding time was considerably increased. The coagulation and clotting times were rarely determined. It is unfortunate that fragility tests were not made on the red blood cells, because this might have been of importance from the standpoint of hemolysis, the yellow color of the skin and the hemosiderosis of the liver, spleen and kidneys.

Even more striking than the reduction in the number of red cells and the percentage of hemoglobin was the leukopenia, which was persistent and progressive to the time of death. With this progressing leukopenia, there was always a marked relative lymphocytosis. The polymorphonuclear neutrophil count always fell below 12 per cent; in fact, in four cases, as low as 1 per cent. No eosinophils, basophils, myelocytes or myeloblasts were seen, except as an extreme rarity in one count in each of three cases. In many instances, oxidase stains were made of the blood, and they coincided closely with the regularly stained blood smears. Pappenheim [1] pointed out that lymphocytes never give a positive oxidase stain, and that some of the early unripe cells of the myelocytic series fail to give a positive oxidase stain and so may be confused with lymphocytes.

1. Pappenheim: Technik und Methodologie der klinischen Blutuntersuchung, Leipzig, Werner Klinkhardt, 1919.

The relative lymphocytosis was made up mostly of the small lymphocytes, which in most of the cases numbered over 85 per cent of the total cell count. In case 2, the large lymphocytes predominated in all the counts, except the last one, in which the small lymphocytes increased in number to 85 per cent. In case 8 with a total lymphocyte count of 89 per cent, there were never more than 9 per cent small lymphocytes. As far as we could make out, the lymphocytes resembled the mature cells seen in normal blood smears, and no lymphoblasts were found.

DIAGNOSIS

The question of a definite diagnosis is difficult because of the similarity of the clinical observations and of the blood picture to those of several conditions that involve the blood and the blood-forming organs. The clinical picture is one of sepsis with aplasia of the bone marrow.

Aplastic anemia, as commonly described, may be idiopathic or due to known causes, and a fatty bone marrow is one of the pathognomonic observations. Smith,[2] in 1919, reported a case of aplastic anemia in a child and reviewed the literature. Of his collected cases, ten occurred in children 16 years of age or younger. In only three of these was the type of bone-marrow mentioned. In these three, which occurred in patients 6, 11 and 14 years of age, it was given as fatty. In 1922, Herrman[3] reviewed the literature and collected reports of twenty-two cases in children, in eight of which the bone marrow was mentioned, in seven as fatty and in one as hypoplastic. The youngest patient with fatty marrow was 2 years of age. Baar[4] asserted that aplastic anemia in children is rare, and he accepted as authentic few of the reported cases. The cases reported here seem to coincide in clinical course and blood picture with the group classified as aplastic anemia, having a short severe course, with high fever, fatal termination, marked anemia, with little or no regeneration of the blood, leukopenia, with a relative lymphocytosis, decreased platelet count, with hemorrhages into the skin, and increased bleeding time. In our three cases coming to post-mortem examination, however, the bone-marrow was red instead of yellow.

Aleukemic leukemia may be easily differentiated, if at some phase there has been a high leukocyte count or if myeloid cells are found in the blood stream. Baar believed that aleukemic leukemia is more

2. Smith, L. W.: Report of an Unusual Case of Aplastic Anemia, Am. J. Dis. Child. **17**:174 (March) 1919.

3. Herrman, Charles: Idiopathic Aplastic Anemia, Am. J. Dis. Child. **23**: 484 (June) 1922.

4. Baar, H.: Ueber akute aleukozytämische Leukämie im Kindesalter, Jahrb. f. Kinderh. **105**:1 (Jan.) 1924.

common in childhood than is aplastic anemia. He also brought out that lymphatic leukemia is often accompanied by the blood changes of aplastic anemia. He considered this, not as a combination of the two diseases, but as an aplasia secondary to the leukemia. Frequently, only postmortem observation of lymphatic metaplasia and infiltration of organs and tissues differentiates aleukemia from other conditions with leukopenia. Our cases show minor differences, which, however, are insufficient, except in cases 1, 2 and 9, to differentiate the observations absolutely from the usual ones of aleukemia leukemia. In none of our cases were there signs of regeneration of the blood, as evidenced by nucleated red cells and myeloid cells or any changes in the lymphatic cells themselves, some of which are commonly found in the aleukemias. At no time, except during the last five days of life in case 2, were there ulcerations or sloughing areas in the mouth, which are common in leukemia.

Essential thrombopenia must also be considered in the diagnosis. The resemblance to this condition is principally to its late stages when the regenerative powers of the blood-forming organs have been exhausted. The initial change is one effecting a reduction in the number of blood platelets, with severe anemia and leukopenia as a secondary change. Hemorrhages in our cases were always late phenomena, occurring only after the child had been ill for some time. In none was there a history of the recurrent large hemorrhages, either in the skin or elsewhere in the body, that are so regularly found in thrombopenia.

Myelophthisic anemia is due to an invasion of the bone-marrow by neoplastic tissue, which gradually crowds out the blood-forming tissue. These children presented no clinical evidence of malignancy, and in none were any such abnormal elements found in the blood stream. Also when the clinical picture in myelophthisic anemia is considered, one expects to find evidence of a regeneration of blood cells rather than complete aplasia.

Malignant endocarditis might also enter into the differentiation, because of the presence of septicemia with petechial hemorrhages, severe anemia and leukopenia. In the three postmortem examinations, there was no evidence of endocarditis. Systolic murmurs were present in eight cases, but there was no increase in the second pulmonic sound. There was nothing in the histories to indicate a previous chorea or rheumatism, although in half of the cases joint pains were present that in no way resembled those of rheumatic fever.

Agranulocytic angina was first described by Schultz [5] in 1922 as a disease that occurs in women and that is characterized by ulcerations of

5. Schultz, W.: Ueber eigenartige Halserkrankungen, Deutsche med. Wchnschr. **48**:1495, 1922.

sloughing areas in the mouth, fever, slight jaundice, rapidly developing exhaustion, leukopenia with a relative lymphocytosis and an almost complete lack of involvement of the red cells and platelets. Since the original description, cases have been reported with hemorrhagic symptoms, marked reduction of the number of red cells and platelets and with necrotizing lesions in locations other than the mouth. The condition has rarely been reported as occurring in children. It is still a much disputed point whether agranulocytic angina is a clinical entity or simply a symptom complex. We incline toward the latter view. The cases here reported certainly bear a close relationship to this condition, differing really in only one point; the absence of necrotizing lesions in the mouth or elsewhere, except in case 2, in which ulcers occurred in the mouth five days before death. It is felt by some that these necrotizing lesions are a secondary infection, and it is possible that this may explain their absence, although there is nothing to bear this out.

Pernicious anemia is common in adult life, but seemingly extremely rare in children. Thursfield [6] referred to aplastic anemia and pernicious anemia as one and the same. Certainly there seems to be no relationship between the cases reported here and pernicious anemia as it is seen in adult life, unless it might be in the terminal stages of the latter, in which there are aplastic blood changes due to exhaustion of the bone-marrow.

COMMENT

From the foregoing summary it can be seen that the cases reported here form a rather definite clinical picture and offer similar blood pictures. However, diagnosis by a definite term or classification is difficult. Postmortem examination of all the cases would have eliminated at least some of the possibilities considered in the differential diagnosis.

The clinical syndrome is one of sepsis with blood changes that have the appearance of aplasia. This is often found in septicemia, but usually the blood shows more evidence of regeneration. The three cases in which the cultures of the blood were positive for bacteria can be looked on with suspicion. Because of the negative blood cultures it does not seem that the other cases could be on the basis of an ordinary septicemia.

Baar pointed out that aplastic anemia should not be confused with the aplastic anemic blood changes that occur in other conditions. Experimental evidence shows that such substances as benzol, arsenic, saponin, ricin, toxins, such as hemolytic streptococcus serum, and the x-rays will produce aplastic anemic blood changes, but that on withdrawal of these agents the normal condition of the blood returns. The aplastic blood picture may appear as a result of infections, neoplasms, repeated hemor-

6. Thursfield, Hugh; and Paterson, Donald: Diseases of Children, ed. 2, New York, William Wood & Company, 1929, p. 456.

rhages and certain parasitic infestations. It is also firmly believed by many that some unknown toxins or noxa may act as the etiologic element.

From a study of our cases and of the literature, it seems that there is no one etiologic agent that can produce the conditions described here, but that any one of several by their action may produce a similar condition varying as to clinical picture and blood picture according to the part of the hematopoietic system affected: the erythrocytic and granulocytic, the lymphatic or the thrombocytic. The terminal picture in all may be similar.

No form of treatment seemed to be of any help. Therapy included intravenous or intramuscular transfusions of blood, administration of iron by injection and by mouth, even intravenous injections of gentian violet and mercurochrome and treatment with horse serums.

CONCLUSIONS

Ten cases of the clinical syndrome of a sepsis, with severe anemia, thrombopenia and agranulocytic leukopenia are reported.

Their relationship to aleukemic leukemia, aplastic anemia, agranulocytic angina and other conditions is discussed.

THE PREPARATION OF DEXTROSE FOR PARENTERAL INJECTION *

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The injection of dextrose parenterally has become a recognized therapeutic measure, notwithstanding the fact that at times its administration is followed by unpleasant reactions. Williams and Swett,[1] in a series of studies on the hydrogen ion concentration of various fluids commonly administered intravenously, found that the p_H of a solution of dextrose became acid on autoclaving, and they attributed the untoward reactions to the injection of this fluid. The same authors, in conjunction with Mellon, Slagle and Acree,[2] advocated the addition of buffer solutions to the autoclaved dextrose as a means of maintaining a neutral solution. This method has been widely adopted, and the results following the use of solutions so prepared seem quite satisfactory. However, the preparation of the buffer salts is a laborious and time-consuming task and has been relegated to those commercial laboratories that supply buffer salts with ampules of 50 per cent dextrose solution. Sanford and Heitmeyer [3] and Grulee and Sanford [4] said that for intraperitoneal injection even buffered solutions of dextrose gave undesirable reactions at times, and they devised the method of dry sterilization of the dextrose over calcium chloride and dissolving just before use. This method seems to have given excellent results, and was later modified by Shohl and Beal [5] so that the method of preparation was less complex and more reliable. I have devised a third method which I feel is the most simple and has some advantages over other methods of preparation.

AUTHOR'S METHOD

Test tubes 6 by 3/4 inches (15.2 by 9.5 cm.) are heated near the open end in a Bunsen flame and drawn out so that they present a constriction near the mouth.

* Submitted for publication, March 19, 1930.

* From the Harriet Lane Home of the Johns Hopkins Hospital and the Department of Pediatrics of the Johns Hopkins University.

1. Williams, J. R., and Swett, M.: Hydrogen Ion Concentration Studies, J. A. M. A. **78**:1024 (April 8) 1922.

2. Mellon, R. R.; Slagle, E. A., and Acree, S. F.: Practical Applications of Buffers, J. A. M. A. **78**:1026 (April 8) 1922.

3. Sanford, H. N., and Heitmeyer, P. L.: Intraperitoneal Use of Dextrose in Treatment of Diseases of Children, J. A. M. A. **90**:737 (March 10) 1928.

4. Grulee, C. G., and Sanford, H. N.: The Use of Dextrose Intraperitoneally in Infants and Young Children, Am. J. Dis. Child. **36**:455 (Sept.) 1928.

5. Shohl, A. T., and Beal, F.: Preparation of Dextrose for Intraperitoneal Injection, Am. J. Dis. Child. **38**:943 (Nov.) 1929.

Into these, 10 Gm. of chemically pure dextrose is poured and allowed to run through the constriction into the tube. The constricted part is then sealed off in the Bunsen flame, so that the dextrose is hermetically sealed in an ampule. Ampules so prepared are sterilized by boiling in the water bath for thirty minutes on each of three consecutive days. When sterile, the ampules may be kept indefinitely, and are made into solution for use simply by dissolving the contents of one ampule in a flask containing the required amount of sterile distilled water. In practice, I have found it advantageous to keep on hand a supply of flasks containing 200 cc. of sterile distilled water. The contents of an ampule dissolved in one of these yields 200 cc. of 5 per cent dextrose solution ready for use; two ampules are dissolved if a 10 per cent solution is required. The dextrose dissolves almost immediately.

Before the ampules of dextrose so prepared were used they were tested in a variety of ways to insure their reliability for clinical use. In order to confirm their sterility, both aerobic and anaerobic cultures were made from the contents

*Table Showing the Effect of Autoclaving and Standing on p_H of Various Solutions.**

	Before Autoclaving	After Autoclaving	One Day After Autoclaving	Two Days After Autoclaving	Five Days After Autoclaving	Seven Days After Autoclaving	Fourteen Days After Autoclaving	Twenty-Two Days After Autoclaving	Thirty-Eight Days After Autoclaving
Autoclaved stock; dextrose 5%	6.4	4.5	4.6	4.6	4.8	4.6	4.7	4.8	4.6
Physiologic solution of sodium chloride	6.3	7.0	6.8	6.7	6.7	6.7	6.7	6.7	6.4
Distilled water	6.4	7.0	6.8	6.6	6.7	6.7	6.6	6.7	6.5
Dextrose 5 per cent from ampules using distilled water	6.4	7.0	6.8	6.6	6.7	6.6	6.6	6.7	6.5
Dextrose 5 per cent from ampules using freshly distilled water	6.4	7.0	7.0	6.8	6.9	6.8	7.1	7.0	6.8
Dextrose 5 per cent from unsterile stock crystals	6.3	7.0	7.0	6.8	6.8	6.8	7.1	7.0	6.8

* All p_H determinations were made with the Heinge-Kiett instrument, using colored glass disks and having an accuracy of approximately ±0.2.

of a number of ampules. These were uniformly sterile. Finally, a series of tubes were inoculated with spores of the hay bacillus, notably resistant to sterilization, but these were all sterile after being boiled for only the first thirty minute period in the water bath.

The hydrogen ion concentration of solutions prepared from such ampules was then studied in comparison with solutions prepared by other methods. It was found that a solution of dextrose prepared by the addition of the contents of a sterilized ampule invariably maintained the p_H of the water in which the dextrose had been dissolved; this was also true of dextrose taken unsterilly from the stock bottle. It was concluded, therefore, that the dry dextrose undergoes no change during sterilization that shows itself in an altered hydrogen ion concentration. Furthermore, ampules kept as long as three months after sterilization differ in no respect from ampules freshly prepared, and there seems to be no reason why such a product cannot be kept indefinitely.

In order to test the changes in p_H on standing, solutions of 5 per cent dextrose, physiologic solution of sodium chloride and distilled water were prepared in large flasks. A supply of ampules of dextrose was then prepared as outlined. The p_H of the fluid in the flasks was determined before and after autoclaving and on various days following. The samples were removed from the flasks under sterile precautions. Each time that the p_H of these samples was determined, 5 per cent solutions of dextrose were made from the ampules, both freshly autoclaved water and the water that had been autoclaved at the beginning of the experiment being used. The accompanying table is a compilation of the results. It will be seen that dextrose made by the ordinary procedures becomes acid to a p_H of 4.5 on being autoclaved, and maintains this acidity for at least a month. There is only a slight change in the p_H of physiologic solution of sodium chloride and distilled water either with autoclaving or on standing. Solutions of dextrose prepared from ampules invariably give the neutral p_H of the water used in making the solution.

It is felt, therefore, that this method affords a means of preparing at any time an absolutely fresh solution of dextrose of whatever concentration required. The solution so prepared contains only the simple dextrose and is free from either preservatives or costly buffers liable to deterioration. Such ampules are hermetically sealed, not subject to atmospheric changes, and may be transported for use at will. Their actual preparation is simple and inexpensive; the preparation of the solutions themselves can be effected in a few moments when flasks of autoclaved water are on hand. Moreover, distilled water boiled in a flask for five minutes was as satisfactory as autoclaved water in the preparation of the dextrose solutions. In fact, distilled water the p_H of which has fallen because of the absorption of carbon dioxide in standing, becomes neutral in reaction after boiling a few minutes. In this manner, fresh dextrose solutions may be available for use outside the hospital. Such solutions are quite trustworthy; I have experienced no untoward reactions following their use either intravenously, subcutaneously or intraperitoneally. In fact, in a series of experiments at present under way, the cellular reaction of the peritoneum of rabbits to injection of this solution was found to be a little greater than to a physiologic solution of sodium chloride and considerably less than to dextrose solutions prepared by autoclaving. Furthermore, the preparation of such solutions as dextrose in physiologic solution of sodium chloride for use in the treatment of dehydration is greatly facilitated by this method. Finally, one may feel quite confident that the hydrogen ion concentration of solutions of dextrose so prepared is constant and at the neutral point.

THE PROBLEM OF DENTAL CARIES*

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The widespread interest that has recently arisen in the problem of dental caries has given considerable impetus to the study of this prevalent disease of childhood, and has renewed the hope that its etiology and the means of its prevention may eventually be discovered. Tangible support for this hope may be found in the reports of successful experimental control of the disease which are appearing at frequent intervals in our present-day literature. Such pronouncements are welcomed by all those who are interested in public welfare and in the health of children, for up to the present time no practical means of preventing dental caries has been offered other than that of oral cleanliness, which is of doubtful efficiency. The discovery of some definite means of controlling or preventing this highly prevalent and important disease would be an inestimable boon to mankind.

In an analysis of these recent contributions there appears to be a considerable divergence of opinion as to the nature of the disease in question and as to the rationale of the preventive measures to be employed. As a result of their studies, various investigators have come to diametrically opposed views, each interpreting his observations in terms of a previously conceived theory. To those who are less familiar with the problem and who are interested in the practical means of controlling the disease, these divergencies of opinion and points of view are extremely disconcerting.

In view of the present confusion regarding the mass of conflicting data and theories thus far advanced in the study of dental caries, and in view of the need for a consideration of first principles in the evaluation of the newer concepts of the problem, it is our purpose in this paper to state the known facts and to discuss certain of the newer theories in the light of these truths.

In the consideration of a new problem or a new concept of an old one, it is always most important to review, at the outset, all the related facts that thus far have been ascertained. To these known facts all

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* From the Laboratories of the School of Dentistry, University of Michigan.

new theories and data must fully conform. If they do not, they must be discarded or they will lead to grave error and misapprehension. The following characteristics of the process of dental caries have been generally accepted as facts. To this list, others may be added that are probably true but that are still open to further proof of their verity:

1. Dental caries is a destruction of the hard substance of the tooth by a process the initial stage of which is decalcification by acids.

2. The acids active in caries are not generally distributed in the saliva, but are localized and concentrated on certain areas of the tooth surfaces.

3. Carious lesions occur most frequently in the pits and fissures of the occlusal surfaces and on certain areas of the approximal, buccal and lingual surfaces of the teeth, at which locations there are opportunities for stagnation and the retention of foreign matter. They do not occur on smooth enamel surfaces that are frequently cleansed.

4. All initial lesions of caries contain acid-forming bacteria capable of producing and living in acids of sufficient potential to decalcify the enamel.

5. The hardness or softness of the teeth may affect the rate of progress and extent of caries but does not alone determine its occurrence. Caries, as a rule, runs a more rapid and extensive course in hypoplastic teeth than in the hard and well formed varieties, but instances commonly occur in which the poorest formed teeth are wholly free from the disease.

6. Malhygiene of the mouth frequently favors the inception of dental caries and increases its activity, but alone does not determine its occurrence. Mouths that are habitually unclean are often wholly free from caries and, conversely, mouths that are scrupulously clean may be seriously affected by the disease.

7. The process of dental caries is related to and often determined by certain constitutional states and conditions of bodily health. The nature of these general influences and the manner in which they affect the course of this dental disease are not clearly understood at this time. The following bodily conditions are perhaps best known as systemic factors which either favor or oppose dental caries:

Heredity: There are strong evidences that the tendency toward dental caries or toward an immunity to the disease may be transmitted from parent to child.

Age: Susceptibility to dental caries is clearly influenced by age. Incidence of the disease is known to be highest during the ages from 7 to 20 years. After 20 years of age the tendency to caries is markedly decreased.

Health: It is frequently noted that severe onsets of dental caries follow attacks of general disease and disturbances of bodily health. During pregnancy caries may be unusually active. Children who are undernourished or who are suffering from a general debility are usually especially prone to dental caries.

Racial Influences: Dental caries is more prevalent in certain races than in others. The natives of Africa, South America and the South Sea Islands, the Esquimaux and many other primitive peoples are notably free from the disease, while those who live in the more civilized lands are extremely susceptible to it. There are evidences that the disease often increases in prevalance as people advance in the scale of civilization. It is also observed that when persons migrate from a caries-free nation to a country in which it is prevalent they and their progeny may later develop dental disease. There is no indication that dental caries is an endemic disorder or that it is induced by any climatic conditions. Diet is the

only constant variable between immune and susceptible races which thus far has been recognized.

Bearing in mind these established facts concerning the diseases, we shall consider the newer and more recent theories concerning dental caries. These fall within two general groups or concepts: 1. Dental caries is produced by a specific infection, the presence or absence of which determines the occurrence of the disease. 2. Dental caries is a local manifestation of a general metabolic disturbance induced by a faulty diet and malnutrition. These two concepts which at present seem to be opposed should each be studied in the light of known facts and be reconciled to them. It is possible that when all the facts are known, these two views may not be diametrically opposed but rather may be harmonized into the true solution of the problem.

From various sources reports are appearing that by increasing the calcium, phosphorus and vitamin intake of children, dental caries is wholly prevented and existing lesions are completely arrested. Notable among these have been the writings of Mac Mellanby of England,[1] Sherman Davis of Indianapolis, and Boyd, Drain and Nelson[2] of Iowa City, each of whom has accentuated the importance of vitamin D. Hanke[3] in a recent article stated that in a nutritional survey of 114 persons, dental caries appeared to be more closely related to scorbutic than to rachitic tendencies, and that the feeding of vitamin C is more important than that of vitamin D in the prevention of dental disease. These observers claim that by the several dietary measures employed they have produced an increase in the calcification of the teeth and a hardening of the dentin by which the carious process has been impeded. They concluded that the most important etiologic factor of dental caries is the constitutional status of the tooth itself and the resistance that it may offer to the acids of fermentation. Further, that the most practical measures for the control of caries consist of dietary regulations by which the teeth are increased in calcification. Although these observations were made on very small groups of children and were conducted for but a short period of time, they are most interesting and may prove to be valuable links in the chain of experimental evidence. The conclusions that have been drawn from these observations, however, are open to discussion. If, through dietary measures, caries is checked by reason of the hardening of the teeth, why then do hard and well formed teeth frequently succumb to the disease? Conversely, why are not all poorly formed and soft teeth carious? As we have related,

1. Mellanby, M., and Pattison, C. L.: Brit. M. J. **2**:1079 (Dec. 15) 1928.

2. Boyd, J. D.; Drain, C. L., and Nelson, M. V.: Dietary Control of Dental Caries, Am. J. Dis. Child. **38**:721 (Oct.) 1929.

3. Hanke, M. T.: J. Am. Dent. A. **16**:2263 (Dec.) 1929.

although caries is more prevalent and proceeds more extensively in poorly formed teeth, its occurrence is not always directly proportional to the quality or perfection of the dental structures. It seems more probable, therefore, that any restraint of dental caries that may have been produced by the dietary measures employed has resulted from the alteration of factors in the process other than the hardening of the teeth.

A somewhat similar method of treatment has been employed on a group of children in Los Angeles, by Hawkins who reported [4] that he obtained a complete arrest of caries in these children over a period of from one to two years. He attributed the beneficial effects of feeding calcium and phosphorus not so much to the hardening of the teeth as to the increase of the alkaline reserve and the neutralizing properties of the saliva. He expressed his belief that the highly alkalinized saliva combines with the acids of caries and neutralizes them as fast as they are formed, thus protecting the tooth from harm. Again in this case, we would not question the verity of the data submitted nor minimize the significance of the results obtained, but we are unable to accept the conclusions that have been drawn. The hydrogen ion concentration of the saliva is invariably near the neutral point and in this respect the differences between the salivas of caries-immune and caries-susceptible persons are not sufficient to account for the differences in predisposition to the disease. Furthermore, the salivas of all persons have a buffer reaction and are able to combine with and neutralize weak acids with which they come in contact. Therefore, the salivas of caries-susceptible, as well as those of caries-immune, persons would be capable of preventing dental caries were they enabled to reach the spot at which the acids are being formed. Apparently such is not the case, but rather does this process take place beneath an enveloping film or plaque which protects the acids of caries from dilution and neutralization by the saliva. Thus, the carious action seems to proceed independently of the general salivary status. Finally, we believe that another factor of the process, namely, the bacterial flora, is much more important in its significance than are the variations in salivary neutralizing powers. The basis for this view may be found in the following statement:

Following the work of McIntosh, James and Lazarus-Barlow [5] and of Rodriguez,[6] who found that an organism closely related to *Bacillus acidophilus* is constantly present in the early stages of dental caries, a

4. Hawkins, Harold F.: Dental Decay: Means for its Control, J. Am. Dent. A. **16**:781 (May) 1929.

5. McIntosh, J.; James, W. W., and Lazarus-Barlow, P.: Etiology of Dental Caries, Brit. Dent. J. **43**:728 (Aug. 1) 1922; Brit. J. Exper. Path. **5**:175 (June) 1924.

6. Rodriguez: Mil. Dent. J. **5**:199, 1922.

group in the laboratories of the University of Michigan during the past four years has pursued extensive investigations of the bacteriology of dental caries.[7] In the bacteriologic and clinical survey of several thousand persons of various ages, the following observations were made:

1. An acidogenic and aciduric type of micro-organism, apparently identical with *B. acidophilus,* was found to be present in practically every lesion of active dental caries.

2. This organism, as a rule, is not present in the mouths of persons who are entirely free from dental caries. In such mouths there appear to be conditions that are unfavorable and antagonistic to the growth of the organisms. When *B. acidophilus* cultures are implanted therein, they promptly disappear.

3. Previous to the inception of active caries in the teeth, active proliferation of *B. acidophilus* in the oral cavity can usually be demonstrated.

4. The elimination of *B. acidophilus* from the mouth, either spontaneously or through experimental procedures, is always followed by a complete cessation of dental caries.

5. By the experimental application of cultures of *B. acidophilus* to teeth in the mouth, carious lesions have been produced.

As a result of these observations, the Michigan group is convinced that dental caries is in reality an infective disease, and that the specific organism involved is *B. acidophilus.* No other factor has thus far been ascertained which bears such a constant and intimate relationship to dental caries or which harmonizes so fully with the known facts concerning the disease.

It is obvious that the growth of *B. acidophilus* and the activity of dental caries are not wholly dependent on nor primarily determined by local conditions in the mouth. Clearly, the growth and activity of the specific bacteria of dental caries are governed by many underlying constitutional factors such as heredity, age, nutrition and general bodily health. The general metabolic states concerned with these biologic factors may produce environmental conditions in the mouth that are favorable or unfavorable to the growth and characteristic fermentative activity of the caries-forming organisms.

If the infective theory of dental caries is correct, it follows that practical measures for the control of the disease should be directed toward the elimination of the caries-producing organisms from the

7. Bunting, R. W., and Faith, Palmerlee: The Rôle of B. Acidophilus in Dental Caries, J. Am. Dent. A. **12**:381 (April) 1925. Bunting, R. W.; Nickerson, Gail, and Hard, Dorothy G.: Further Studies of the Relation of B. Acidophilus to Dental Caries, Dental Cosmos **68**:931 (Oct.) 1926. Bunting, R. W.; Nickerson, Gail; Hard, Dorothy G., and Crowley, Mary: Further Studies of the Relation of B. Acidophilus to Dental Caries: II, ibid. **70**:1 (Jan.) 1928. Bunting, R. W.; Crowley, Mary; Hard, Dorothy G., and Keller, Margaret: Further Studies of the Relation of B. Acidophilus to Dental Caries: III, ibid. **70**:1002 (Oct.) 1928.

mouth or toward the establishment of oral conditions that are unfavorable to their growth and activity. To this end three lines of attack are suggested:

1. The attempt to discover in the saliva of caries-immune persons an inhibitory principle that is antagonistic to the growth of *B. acidophilus*, and that when introduced in the oral cavity of susceptible persons would eliminate the organism.

2. The study of the relationship of diet and nutrition to the growth and activity of *B. acidophilus* in the mouth to determine whether or not caries-forming organisms may be controlled by a regulation of the diet.

3. A study of the effectiveness of various prophylactic and therapeutic procedures in eliminating *B. acidophilus* from the mouth.

During the past three years the Michigan group has been conducting preliminary studies of the second and third, namely, dietary and therapeutic, methods of the control of caries. These studies are as yet by no means complete or satisfactory, but rather constitute introductory surveys of the field leading up to much more exhaustive researches that are now being organized and soon will be under way.

DIETARY STUDIES

There are many indications that diet and nutrition play an important part in the problem of dental caries. The first experimental caries was produced in guinea-pigs by Howe[8] by feeding diets deficient in the antiscorbutic vitamin. Later it was observed that dental caries occurred in many of the rats to which McCollum experimentally fed various forms of deficient rations. Rats fed a normal and well balanced diet were not so affected. From a survey of a large number of rat skeletons from McCollum's laboratories, Grieves[9] reported that the caries that occurred in the experimental animals was related to no single dietary deficiency, but was associated with disproportions of calcium and phosphorus or with a lack of essential vitamins in the diet.

These observations were corroborated by animal experimentation in the Michigan laboratories.[10] Rats fed on adequate diets were free from dental caries, but when a part of the requisite calcium or butter fat was withheld from such diets typical caries occurred in the teeth. That the disease was not wholly due to malnutrition and dental formative defects was shown by the fact that in a group of rats fed on a very deficient, carbohydrate-free diet, there was no sign of dental caries. Without carbohydrates, the aciduric organisms could produce no acids of caries nor could they live in the mouths of animals so fed.

8. Howe, Percy: Dental Cosmos **62**:921, 1920.

9. McCollum, E. V.; Simmons, N.; Kinney, E. M., and Grieves, C. J.: Bull. Johns Hopkins Hosp. **33**:202 (June) 1922.

10. Bunting, R. W.: Dental Cosmos **67**:771, 1925.

It was further noted that when a considerable quantity of sugar was given to rats that were fed a diet that was otherwise normal and adequate, dental caries was prevalent. It is probable that the diet was unbalanced by the high carbohydrate consumption as the animals, by choice, ate the sugar before their regular ration.

As we previously stated, the human races that are conspicuously free from dental caries, as a rule, live on a very simple diet in which natural foods predominate. There are indications that the high incidence of the disease among civilized people is related to an unnatural and inadequate dietary regimen.

In a survey of a number of orphanages and children's homes, it was observed by the Michigan group that dental caries is much less prevalent in those institutions in which the children are afforded a good diet than in those in which the food is inadequate. An experimental study of the effect of diet on dental caries was made on two groups of children in orphanages that were maintained on a prescribed diet. Their dental condition was observed over a period of two years. The children were fed a well balanced, well fortified ration in which only minimal amounts of sugar and white flour were included. Each child received 1 quart (946 cc.) of milk and some green vegetables and fruit each day. In the first group of 106 children, 35 per cent of those who gave a positive reaction to *B. acidophilus* gave a negative reaction during the experiment, and in 30 per cent the growth of the organism was variable and low in activity. Among these 106 children there were 84 in whom there was no evidence of active caries.

In the second group of 228 children, 37 per cent of those who had given positive reactions to *B. acidophilus* gave negative reactions and 27 per cent gave variable results. In this group there were 151 children in whom caries appeared to be inactive.

The results of this investigation indicate that the dietary program produced a definite inhibitory effect on the growth of *B. acidophilus* and an arrest of caries in a large proportion of the children under observation. These beneficial effects, however, did not appear in all the children so treated. In certain members of the group, the aciduric organisms thrived in the oral cavity and caries actively disintegrated the teeth. The results of this preliminary dietary experiment in the control of dental caries were, therefore, eminently satisfactory but not as completely so as were later, more carefully controlled experiments.

THERAPEUTIC MEASURES

If, as has been suggested, dental caries is an infective disease and is produced by the overgrowth of specific aciduric types of bacteria, it is possible that the process may be controlled or wholly terminated by

the use of certain antiseptics that may be specially antagonistic to this type of micro-organism.

In a study of this question many drugs and antiseptic preparations have been tested both in the laboratory and clinically. Of these, at the present time, two preparations appear to be most useful, namely, metaphen and hexylresorcinol (S.T. 37). In the laboratory it has been demonstrated that these preparations are not equally effective in all cases, for certain strains of *B. acidophilus* show marked resistance to one or the other of them while others are killed by very dilute solutions of either drug. In many instances organisms that are resistant to one preparation are readily killed by the other.

In a clinical test of metaphen in the control of dental caries it was found that when used as a mouth wash it had no demonstrable effect on the oral *B. acidophilus*. However, when the teeth were polished by a dentist and the metaphen was applied directly to the tooth surfaces *B. acidophilus* was eliminated in from 50 to 60 per cent of cases and in the remainder repeated treatments decreased the growth and characteristic activity of the organisms. Polishing the teeth alone did not eliminate the organism.

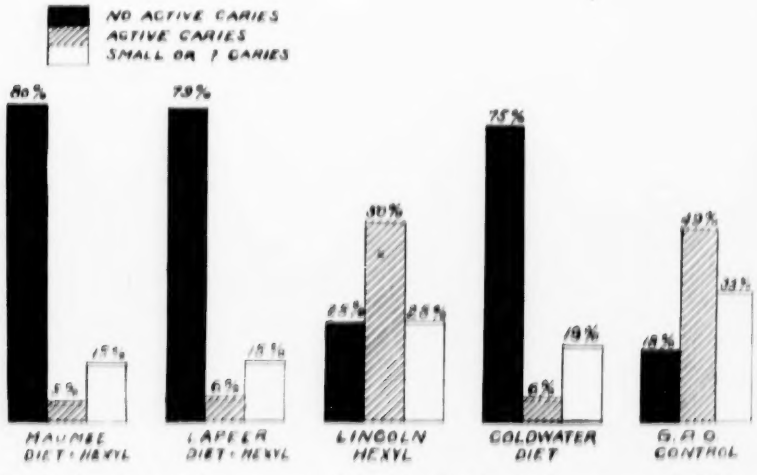
Hexylresorcinol possesses a distinct advantage over metaphen in that it appears to have a greater power of penetrating the bacterial plaques and is more effective in combating *B. acidophilus* when used as a mouth wash. In a preliminary experiment to determine the effect of this drug, a group of thirty-six adults, all of whom gave a positive reaction to *B. acidophilus*, used hexylresorcinol diluted with three parts of water as a mouth wash three times daily without any other prophylactic interference. Twenty-four of these persons gave a negative reaction to *B. acidophilus* in from two to eight weeks.

During the past year a rather comprehensive experiment in the control of dental caries was conducted on three large groups of children in public schools and orphanages. In this experiment certain dietary and therapeutic measures were carried out over a period of one year and the activity of dental caries noted by carefully recorded examinations. In two orphanages—one, the Lucas County Children's Home at Maumee, Ohio, and the other, the Children's Home and Training School at Lapeer, Mich.—groups of children were put on a well fortified diet in which sugar was eliminated except as it was used in cooking to make foods palatable. The diet was a varied ration fortified by the inclusion of 1 quart of milk and some green vegetables and fruit for each child daily. No cod liver oil or viosterol was given. These children had no sugar on their cereals or in their beverages, very little sweetened preserves and pastry, and little or no candy. In addition to the dietary control, hexylresorcinol (S.T. 37) was used daily as a mouth wash, diluted with three parts of water. The object of this experiment was to

determine whether or not by both dietary and therapeutic measures it is possible to produce an appreciable decrease in the amount of caries. At the beginning of the experiment the condition of the teeth was carefully recorded and actual drawings of the approximate size and location of all cavities and fillings were made. Each record was made

Results of Experiments in the Control of Caries

Group	No.	Method	Time	No Active Caries		Active Caries		Small or ? Caries	
				No.	%	No.	%	No.	%
Maumee	156	Diet, hexylresorcinol	1 yr.	125	80	8	5	23	15
Lapeer	118	Diet, hexylresorcinol	1 yr.	93	79	7	6	18	15
Lincoln	104	Hexylresorcinol	9 mo.	26	25	52	50	26	25
Coldwater	159	Diet	1 yr.	119	75	7	6	33	19
G. P. O.	74	Control	1 yr.	13	18	36	49	25	33



Graph, showing relative amounts of dental caries in the five groups of children.

by two dentists, one checking against the other. At the expiration of the year the children were again examined in a similar manner and the dental conditions compared with the records of one year previous. The results obtained from this experiment are set forth in the accompanying table and chart.

Among the 156 children in Maumee who were thus observed, there were 125, or 80 per cent, in whom there was a marked reduction of *B. acidophilus* in the mouth and in whom no vestige of active caries appeared during the year. There were only 8 children, or 5 per cent, in whom caries was active, and in these the disease was limited to but one to three small cavities on the occlusal or buccal surfaces of the teeth, or to slight extensions of previous caries. In the remaining 15 per cent there were only minute dental defects, which, in the opinion

of the observers, were questionable caries. Among the 125 children who had no caries there were 66 who, at the beginning of the experiment, had from one to ten open cavities which remained open throughout the year. At the final examination it was found that they had not increased in size nor were there any new lesions in the teeth. There were 20 children who had filled cavities with no extensions of caries or new caries.

In Lapeer, among 118 children there were 93 who had no new cavities and 7 who showed evidences of active dental disease consisting of from one to three small cavities none of which was extensive. The remaining 18 children had defects which were recorded as questionable caries only. Among the 93 children who had no new caries there were 57 who, at the first examination, had open cavities which were not filled during the year and which did not increase in size. In 12 additional children previous caries were filled, but no new cavities occurred during the year.

To throw some light on the action of hexylresorcinol alone, a group of children in a public school known as the Lincoln Consolidated School were given hexylresorcinol as a mouth wash twice daily five days a week, during a nine months' school term. This was done in the school room as a regular part of the hygiene exercises. No attempt was made to alter the regular diet of these children. At the end of nine months it was found that among 104 children who were included in this experiment there were but 26 who had no caries, and among these were a number of children who might be said to be naturally immune to the disease. In 52 children, or 50 per cent, there were marked evidences of active caries some of which were quite extensive. The clinical picture of this group was very similar to that of the G. P. Orphanage control group and was vastly different from that which was observed in the two other institutions in which both diet and hexylresorcinol were used.

The data obtained from this experiment show clearly that in two groups of children active dental caries was almost completely arrested by the dietary and therapeutic measures employed and that, during the year of observation, the occurrence of this very prevalent dental disease was made almost negligible. It appears that of the two methods employed, control of diet was by far the most active inhibitive force, but it will require other carefully controlled experiments to determine just what parts diet and therapeutic remedies severally play in the prevention of dental caries.

For a year a group of children in the Michigan State Public School at Coldwater, Mich., was under observation. At the first inspection it was observed that these children were remarkably free from dental disease and that their diet was unusually good. The following

analysis of the institutional ration was made by Mary Harrington, dietitian of the Harper Hospital, Detroit:

	Gm.		
Protein	from 50	to	60
Fat	from 60	to	70
Carbohydrates	from 170	to	220
Calories	from 1,500	to	1,800
Calcium	from 0.90	to	1
Phosphorus	from 0.91	to	1
Iron	from 8	to	9

The A, B and C vitamin content of the diet was slightly below the optimum. About 4 teaspoonfuls of sugar were consumed daily, being added to the aforementioned ration. Little or no candy was eaten by the children.

Although this diet was not ideal, the excellence of the general and dental health of the children warranted its continuance without material change for one year, during which time the activity of dental caries might be recorded. At the end of one year 159 children were reexamined, and among them there were 119, or 75 per cent, who had no evidence of active dental caries. There were no new cavities in the teeth in this group, nor were there any extensions of open cavities which had remained unfilled throughout the year. Caries appeared to be active in only 7 children and consisted of but one to three small cavities or extensions of previous lesions. In the remaining 33 children dental caries was very slight or questionable.

In studies of this character, it is exceedingly difficult if not impossible to obtain control groups that are fully satisfactory. For one year a group of 74 children was observed in the G. P. Orphanage, where the diet was apparently not carefully balanced, and where the children obtained considerable candy. No alteration was made in the diet, nor was any preventive treatment given. At the end of the year it was found that 13 of this group had no new dental caries but that 36, or 49 per cent, had pronounced dental lesions. There were also 25 who had small or questionable caries.

CONCLUSIONS

The foregoing records of preliminary studies in the control of dental caries strongly suggest that an adequate and well balanced diet tends to reduce greatly or to arrest entirely the progress of the disease. In the Maumee, Lapeer and Coldwater groups, in which fairly adequate diets were provided, active caries was almost negligible and old lesions were uniformly arrested. In the Lincoln and G.P.O. groups, in which the diets were not as carefully planned, dental disease was active and rapid in its course. Although these studies were crude and far from

exact in detail, the records show that dental caries was controlled in three large groups of children for one year. These results are so gratifying that further carefully planned dietary studies of a similar nature will be undertaken in the near future.

In this paper an attempt has been made to summarize and to correlate the various points of view in regard to this common disease of children. It is interesting to note that, notwithstanding the variance of opinions, the students of this problem have independently arrived at almost identical conclusions regarding the dietary control of the disease. Practically all concur in the opinion that an adequate, well balanced diet is apparently inhibitive to dental caries. Whether they believe that the control of caries occurs as the result of a decrease of aciduric bacteria in the mouth, the increase of salivary alkalis or the hardening of the tooth is not so important as the fact that the exponents of each theory advocate practically the same form of dietary procedure. The diet prescribed by the Michigan group was fortified by milk and green vegetables, but sugar was eliminated as far as possible, each child in the Maumee school receiving a total of one-third pound (151.2 Gm.) a month. The reduction of sugar was based on the assumption that the average child consumes too much carbohydrate in the form of candy and highly sweetened foods, as a result of which the appetite for other foods is perverted and a state of nutritional unbalance is produced; furthermore, that candy and sticky confections retained about the teeth afford a most favorable pabulum for acid fermentations in the mouth. Whether or not all may agree with the rationale of this procedure, it is interesting to note that the children so fed grew normally, were in good health and were notably free from common colds and other infectious diseases. Also, dental caries was almost completely arrested.

It must be borne in mind, however, that the studies that have been reviewed are still in their early stages, and that much work still remains to be done before any definite conclusions may be drawn. The fact that dental caries is frequently checked by the feeding of a normal diet does not prove that the disease is wholly due to malnutrition. There are many factors in the metabolic state, which may be equally important in the control of dental caries. These questions may be solved only by well qualified workers in the fields of bacteriology, chemistry, nutrition and other allied sciences to which this problem is related.

SUMMARY

1. In the study of the cause and control of dental caries there is need for a fuller understanding of basic facts concerning the disease which have already been established. Many theories have been advanced which are not in accord with known facts.

2. Evidence is given in support of the view that dental caries is a specific infective process, the activity of which is dependent on certain metabolic states.

3. As the result of dietary and therapeutic experiments, active dental caries was reduced to a negligible quantity in 433 children. Of the methods employed, dietary measures appeared to be the most important.

4. The diets prescribed for the control of dental caries were well balanced, well fortified, adequate rations in which sugar was reduced to the minimum.

DIFFUSIBLE BLOOD SERUM CALCIUM IN NORMAL NEW-BORN INFANTS*

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AND
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Calcium exists in the blood serum in three forms: in an ionized state, in an un-ionized but diffusible or dialyzable form and in an un-ionized, nondiffusible combination.[1] The evaluation of the part played by these fractions in the body metabolism is not fully understood. One of the underlying reasons for this failure to evaluate the rôle of these fractions properly has been the lack of standardized methods for their determination, and consequently insufficient data as to their normal values. Several studies on the diffusible serum calcium in animals and in human adults have appeared,[2] but it is our belief that no work has been done that deals with normal values for the calcium partition in the new-born infant.

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* This is one of a series of biochemical studies in infancy made possible by a grant from the Knox Gelatin Company, Johnstown, N. Y.

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METHODS AND EXPERIMENTAL PROCEDURE

Observations were made on fifty normal new-born infants, ranging from 5 to 22 days in age. Of this group, twenty-four were boys and twenty-six girls. Blood was drawn from three to four hours after the last feeding, and as many various determinations as possible were made on the same sample of serum. From 15 to 20 cc. of blood was obtained from the fontanel and allowed to clot in specially cleaned, sterile test tubes and the serum was separated by centrifugation; 3 cc. of serum was measured into dry collodion membrane sacs[3] and subjected to ultrafiltration for three hours, according to the technic of Greenberg and Gunther.[4] The diffused calcium was then determined in an aliquot portion of the ultrafiltrate by the van Slyke gasometric procedure.[5] From this determination the total diffusible calcium in the blood serum was estimated according to the method described by Greenberg.[6]

Total calcium was determined on a 1 cc. portion of the serum according to the method of Kramer and Tisdall;[7] the supernatent fluid from this was utilized for the inorganic phosphate determinations as suggested by Gunther and Greenberg.[8]

Protein determinations were carried out by the Greenberg modification of Howe's method.[9] Globulin and albumin fractions were determined separately, and the sum of these two was taken as the total protein. The technic of van Slyke[10] was employed to determine the serum chlorides.

Cholesterol was estimated on whole blood by the method of Bloor.[11] Oxalated whole blood was taken for this determination at the same time the blood was drawn for the serum determinations.

RESULTS

Total calcium determinations on thirty-two infants gave an average of 11.4 mg. per hundred cubic centimeters of serum. Variations ranged from 9.3 to 12.4 mg. The distribution is shown in the accompanying illustration (*A*). The average for seventeen boys was 11.1 mg.,

3. These sacs were poured from a freshly opened can of collodion.

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7. Tisdall, F. F.: A Note on the Kramer-Tisdall Method for the Determination of Calcium in Small Amounts of Serum, J. Biol. Chem. **56**:439 (June) 1923.

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9. Greenberg, D. M.: The Colorimetric Determination of the Serum Proteins, J. Biol. Chem. **82**:545 (May) 1929.

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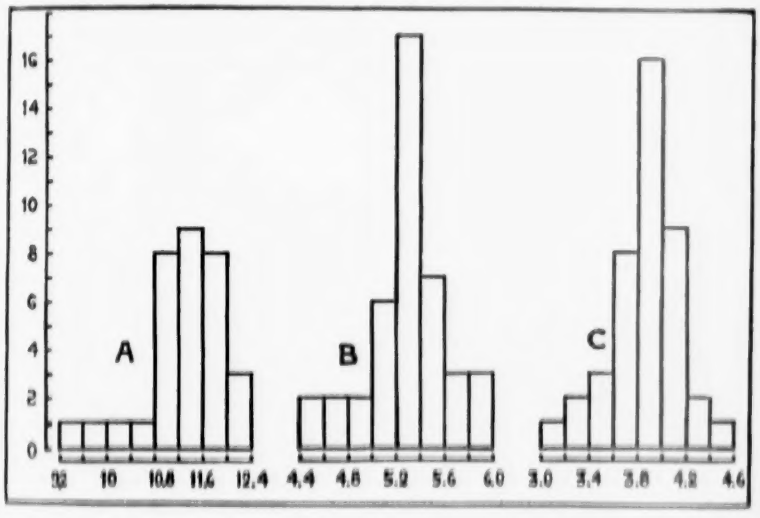
and that for fifteen girls, 11.6 mg. These figures do not suggest a marked difference in total calcium in relation to sex.[12] The average total calcium is a little higher than that reported for adults by various workers.[13] Marriott and Howland [14] recorded 11 mg. as an average for the serum calcium of normal infants up to 3 months of age.

In forty-two cases the calcium per hundred cubic centimeters of ultrafiltrate averaged 3.8 mg. The frequency distribution is shown in the chart (*C*). Since these results were obtained by an admittedly empiric method, and as the diffusible calcium is calculated from the determined ultrafiltrate calcium, this value is probably the most significant figure.



Frequency distribution of (*A*) the total calcium, (*B*) the diffusible calcium in the serum and (*C*) the diffusible calcium in the filtrate.

The diffusible serum calcium in forty-two infants averaged 5.3 mg. per hundred cubic centimeters of serum, the lowest diffusible calcium being 4.4 and the highest 6 mg. The frequency distribution (*B* in chart)

12. Lyman, H.: The Calcium Content of Human Blood, J. Biol. Chem. **30**:1, 1917.

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14. Marriott, W. M., and Howland, J.: Observations upon the Calcium Content of the Blood in Infantile Tetany and upon the Effect of Treatment by Calcium, Quart. J. Med. **11**:289 (July) 1917.

TABLE 1.—*Determinations of Calcium, Inorganic Phosphates, Protein Fractions, Chlorides and Cholesterol on Fifty New-Born Infants*

Case	Patient	Age, Days	Sex	Ultrafiltrate of 3 Cc. of Serum: Cc.	Ultrafiltrate of 3 Cc. of Serum: Per Cent	Mg. of Calcium per 100 Cc. of Serum: Ultrafiltrate	Mg. of Calcium per 100 Cc. of Serum: Total	Mg. of Calcium per 100 Cc. of Serum: Diffusible*	Mg. of Calcium per 100 Cc. of Serum: Nondiffusible	Diffusible Calcium, per Cent of Total	Inorganic Phosphorus	Serum Proteins, Grams per 100 Cc.: Total	Albumin	Globulin	Chlorides, Mg. per 100 Cc.	Cholesterol of Whole Blood	Comment
1	Ben.	7	F	1.51	50	4.98	9.93	5.83	4.10	58.70	4.82	6.96	4.53	1.73	608	321	
11	Sch.	9	M	1.65	55	4.28	10.40	5.95	5.45	52.19	4.47	6.88	5.01	1.87	624	....	
12	Par.	15	F	1.70	56.6	4.94	10.00	5.58	5.42	50.73	4.50	7.27	5.36	1.91	595	....	
13	Osl.	7	M	1.65	55	4.91	10.00	5.60	5.40	50.90	4.59	7.20	5.04	2.16	602	....	
15	Kos.	12	M	1.75	58.3	5.81	10.80	5.19	5.61	48.09	5.34	6.94	4.95	1.99	626	....	
16	Eis.	8	F	1.70	56.6	4.36	10.40	5.74	5.66	50.35	4.41	6.74	4.73	2.01	654	....	
24	Ros.	6	F	2	66.6	4.52	10.00	5.93	6.07	49.42	4.56	7.42	5.35	2.07	623	154 S	Jaundiced serum
25	Bur.	9	M	1.70	56.6	5.68	10.59	5.02	6.18	44.82	5.06	7.35	5.32	2.03	635	321 S	
26	Kno.	8	M	1.70	56.6	5.67	10.40	5.06	5.74	46.85	4.92	6.98	5.14	1.84	....	162	
27	Har.	10	F	1.65	55	5.98	10.40	5.57	5.83	49.73	4.67	6.81	5.09	1.72	615	108 S	
28	Jon.	8	F	1.85	61.6	5.98	10.60	5.19	6.41	44.74	4.85	6.89	5.11	1.78	627	....	Slightly colored ultrafiltrate
5	Gre.	10	F	1.60	53.3	5.94	....	5.55	....	48.94†	....	6.82	5.05	1.77	....	....	
7	Hig.	10	F	1.80	60.0	5.97	....	5.28	....	46.39†	....	6.78	4.98	1.80	....	156 S	
8	Tri.	9	M	1.65	55.0	5.72	....	5.21	....	45.78†	....	7.06	4.85	2.21	....	142 S	
9	Scog.	10	M	1.75	58.3	4.58	....	5.97	....	52.47†	....	7.83	5.64	2.19	595	174 S	
18	Lot.	7	F	1.75	58.3	5.81	....	5.19	....	45.60†	....	6.41	4.80	1.61	....	....	
19	Jar.	7	M	1.70	56.6	5.67	10.80	5.06	5.74	46.85	5.26	....	....	....	....	136	
29	Sco.	12	M	1.63	54.3	5.98	10.40	4.69	6.71	41.14	4.93	....	....	....	592	149	Crying
30	Bell	10	M	1.68	56.0	5.80	10.0	5.39	6.61	44.91	5.08	....	....	....	586	156	
31	Seib.	11	F	1.58	52.7	5.98	12.5	5.10	7.30	41.12	5.57	....	....	....	592	189	
32	Seim.	11	M	1.64	54.6	5.57	11.80	4.72	7.08	40.0	4.84	....	....	....	586	142	Crying
33	Noon	9	F	1.38	46.0	4.57	12.40	5.62	6.78	45.32	4.78	....	....	....	598	126	
34	Gil.	6	M	1.58	52.6	5.67	12.0	4.38	7.62	36.51	5.12	....	....	....	609	....	Excessive crying
40	Gue.	11	M	1.56	52.0	5.52	11.40	5.02	6.38	44.03	5.46	....	....	....	....	129	
42	Mor.	13	F	1.65	55.0	5.80	10.60	5.43	5.17	51.22	4.82	....	....	....	....	118	
43	Lew.	11	M	1.68	56.8	5.78	10.80	5.29	5.51	48.99	5.10	....	....	....	....	141	
44	Wea.	12	M	1.65	55.0	5.82	10.80	5.35	5.45	49.53	5.00	....	....	....	....	123	
45	Hal.	9	M	1.65	55.0	5.85	10.32	5.32	5.01	51.50	4.83	....	....	....	....	187	
46	Rob.	22	F	1.22	40.6	5.07	11.00	5.08	5.92	48.96	5.58	....	....	....	....	170	
47	Bol.	9	F	1.49	49.6	5.85	11.40	4.98	6.42	43.68	5.61	....	....	....	....	200	
48	Rose	8	F	1.58	52.3	5.94	12.20	5.33	6.87	43.68	5.54	....	....	....	....	....	
49	Rud.	8	F	1.72	57.3	5.97	12.20	4.41	7.79	36.15	5.61	....	....	....	....	....	Crying
35	Nei.	19	F	1.68	56.0	5.78	12.40	5.24	7.16	42.25	....	....	....	....	....	....	
36	Scho.	16	F	1.68	56.0	5.98	12.20	5.52	6.68	45.24	....	....	....	....	....	....	
37	Gax.	19	M	1.73	57.6	5.70	12.80	5.07	6.73	42.96	....	....	....	....	....	....	
20	Gom.	10	M	1.72	57.3	5.98	12.30	5.39	5.93	48.43	5.24	....	....	....	....	134	
21	Vill.	5	F	1.77	59.36	5.93	....	5.43	....	47.71†	....	7.83	5.64	2.19	635	....	
22	Bor.	8	F	1.70	56.6	5.96	....	5.35	....	46.13†	....	7.41	5.41	2.00	....	....	
38	Bar.	10	M	1.67	55.6	5.95	....	5.32	....	46.74†	....	....	....	....	....	....	
39	Reg.	10	M	1.58	52.3	5.78	....	5.36	....	47.10†	....	....	....	....	....	....	
50	Sher.	10	F	2.05	68.3	6.07	....	5.25	....	45.96†	....	....	....	....	....	....	17 hours ultrafiltration
51	Hor.	7	M	1.98	66.0	5.85	....	4.92	....	43.24†	....	....	....	....	....	....	17 hours ultrafiltration
2	Due.	7	M	....	....	....	9.55	....	....	....	4.56	6.54	4.61	1.72	628	....	
3	Hol.	9	F	1.84	61.3	....	....	....	....	....	....	7.18	5.34	1.64	596	....	Leak in membrane
4	Mur.	10	M	1.85	61.6	....	....	....	....	....	....	7.27	5.57	1.70	590	....	Leak in membrane
6	McC.	7	F	1.65	55.0	....	....	....	....	....	....	6.94	5.14	1.80	....	140	Leak in membrane
10	Kie.	7	F	1.67	55.6	....	....	....	....	....	....	7.19	5.09	2.10	....	....	
14	Ari.	10	F	1.55	51.6	....	....	....	....	....	....	7.05	4.98	2.07	597	....	
17	Pur.	7	F	1.65	55.0	....	....	....	....	....	....	6.93	5.13	1.80	595	....	
23	Her.	5	M	1.79	59.3	....	....	....	....	....	....	7.44	5.44	2.00	627	150 S	Leak in membrane

* This column was calculated by multiplying a correction of 0.35 cc. as the volume of serum protein in the 3 cc. of serum used, subtracting and reading. † Biol. Chem. J., 1921, lvi, 481.

‡ These were calculated from an average base excess of 45.6 mg. per hundred cubic centimeters of serum.

6	McC.	7	F	3.65	25.0				7.24	5.56	1.70	590		Leak in membrane
10	Kle.	7	F	3.67	25.0				6.98	5.14	1.80		140	Leak in membrane
14	Ari.	10	F	3.55	25.0				7.19	5.00	2.10			
17	Pur.	7	M	3.60	25.0				7.05	4.98	2.07	595		
23	Her.	5	M	3.70	25.0				6.91	5.31	1.80	595		
									7.44	5.44	2.00	625	150.8	Leak in membrane

* This column was calculated by making a correction of 0.04 cc. as the volume of serum protein in the 2 cc. of serum used (according to Hiscox, Austin and Greenberg, J. Biol. Chem. 85:141 [Jan.] 1930).

† These were calculated from an average total serum of 10.0 gm. per hundred cubic centimeters of serum.

TABLE 2.—*Summary of Observations in Table 1*

	Mg. of Calcium per 100 Cc. of Serum				Diffusible Calcium, per Cent of Total		Inorganic Phosphorus	Serum Proteins, Grams per 100 Cc.			Chlorides, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	
	Ultrafiltrate	Total	Diffusible	Nondiffusible	Uncalculated	Calculated		Total	Albumin	Globulin	Serum	Whole Blood	Serum
Total	760.97	363.81	222.68	190.73	1,438.79	516.66	145.32	383.20	222.48	49.72	14,548	2,693	984
Number of cases	42	32	42	31	31	11	29	26	26	26	24	17	7
Mean average	3.52	11.37	5.30	6.15	46.42	46.91	5.01	7.04	3.53	1.51	606	148	140
Standard deviation, $\sigma = \sqrt{\frac{\Sigma d^2}{(n-1)}}$ (Scott, E. L.: J. Biol. Chem. 73:81 [May] 1927)	0.27	0.74	0.36	0.82	4.82	2.22	0.37	0.29	0.20	0.18	12.6	26.8	18.9
Probable error single observation, $\pm 0.6745\sqrt{\frac{\Sigma d^2}{(n-1)}}$ (Dunn, H. L.: Physiol. Rev. 9:275 [April] 1929)	0.18	0.50	0.25	0.55	3.25	1.56	0.25	0.20	0.13	0.12	9.16	19.4	12.7
Probable error of the mean, $\pm 0.6745\sqrt{\frac{\Sigma d^2}{n(n-1)}}$ (Dunn)	0.03	0.09	0.04	0.10	0.58	0.47	0.05	0.05	0.04	0.02	1.95	4.71	4.81

* Σ represents sum of, d the difference between the individual observations and the mean of the series, and n the total number of observations in a series.

shows that 71 per cent of the determinations are between 5.0 and 5.6 mg. Statistically, 76 per cent of the results lie within one standard deviation of the mean and 98 per cent lie within two standard deviations from the mean. Sex does not seem to influence the diffusible calcium, as 5.2 mg. was obtained as an average for twenty-one boys and 5.4 mg. for twenty-one girls.

In thirty-one cases in which the figures for both the total and the diffusible calcium are available the percentage of calcium in diffusible form represents 46 per cent of the total calcium. If we substitute our average total calcium figures in the eleven cases in which only the diffusible calcium was estimated, the calculated percentage of the diffusible fraction to the total is 46.9 per cent. Averaging both the calculated and the uncalculated cases, one finds the average percentage for the diffusible calcium in forty-two cases to be 46.7 per cent. This is a little lower percentage than is found in adults.[15]

Inorganic phosphate determinations in twenty-nine cases gave an average of 5 mg. per hundred cubic centimeters of serum, with a variability of from 4.4 to 5.6 mg. These observations are within the range of normal.[16]

Determinations of serum protein were made in twenty-six cases. It has been considered that the nondiffusible calcium is combined with one of the protein fractions, probably albumin.[17] A possible correlation between the partition of the protein and the nondiffusible calcium was therefore sought. The serum albumin averaged 5.1 Gm., and the serum globulin 1.9 Gm. per hundred cubic centimeters of serum. The nondiffusible calcium was found to be 6.2 mg., or 53.6 per cent. While it appears that the averages for both the serum albumin and the nondiffusible calcium are high normals, no correlation could be obtained from the individual cases.

An average of 606 mg. per hundred cubic centimeters of serum was found in twenty-four determinations of serum chlorides. Serum chlorides are usually higher in infants than in adults.[18]

Seventeen determinations of cholesterol on the whole blood were obtained, and ranged from 116 to 189 mg. per hundred cubic centimeters. An average of 148 mg. for these cases was found. These values are

15. Liu, S. H.: The Partition of Serum Calcium into Diffusible and Non-Diffusible Portions, Chinese J. Physiol. **1**:331 (July) 1927.

16. Howland, J.: The Etiology and Pathogenesis of Rickets, Medicine **2**:349 (Nov.) 1923.

17. Greenberg, D. M.: The Electrical Transference of Calcium in Blood Serum Protein Solutions, J. Biol. Chem. **79**:477 (Sept.) 1928. Marrack, J., and Thacker, G.: The State of Calcium in Body Fluids, Biochem. J. **20**:580, 1926.

18. Myers, V. C.: Chemical Changes in the Blood and Their Clinical Significance, Physiol. Rev. **4**:274 (April) 1924.

lower than those reported by Goldbloom and Gottlieb,[19] but correspond with the figures given by Slemons and Curtis.[20] Seven determinations of the serum cholesterol were made and averaged 140 mg. per hundred cubic centimeters of serum.

COMMENT

In view of the work that has been done on the state in which calcium exists in the blood serum and in the body tissues, it is evident that isolated determinations of the total serum calcium are of questionable clinical value. Certain clinical facts and symptoms related to calcium disturbance can only be interpreted when the partition of calcium is known. Nephrosis, kala-azar, infantile tetany and the tetany of parathyroid deficiency have all shown pathologic variations in calcium partition.[15] The standardization of methods for the determination of the calcium fraction will do much to encourage clinical investigation into a variety of other conditions. Although these methods may be empiric and yield only empiric results, such results are of demonstrable clinical use.[21]

It would appear from the data obtained in this study that in infants the average number of milligrams of diffusible calcium per hundred cubic centimeters of serum is about the same as normal amounts obtained in adults. Because of the slightly higher total calcium in infants, the percentage of the diffusible calcium as related to the total calcium is a little lower than in adults.

In the cases reported here no significant statistical correlation could be determined between the total calcium or the diffusible fraction and the inorganic phosphates, protein fractions, chlorides or cholesterol. The variations on both sides of the averages are about equal. As these cases are all those of normal new-born infants with values for all determinations made being well within accepted normal standards, it is not to be expected that a definite statistical correlation would be found between the various factors mentioned.

SUMMARY

Studies of calcium partition in the blood serum of fifty new-born infants, ranging from 3 to 22 days in age, are reported, together with determinations of the serum inorganic phosphates, chlorides and protein fractions and the whole blood cholesterol.

19. Goldbloom, A., and Gottlieb, R.: The Cholesterol Content of the Blood of Infants and Children, Canad. M. A. J. **17**:1333 (Nov.) 1927.

20. Slemons, J. M., and Curtis, C. S.: Cholesterol in the Blood of Mother and Fetus, Am. J. Obst. **75**:569 (April) 1917.

21. Studies on the partition of serum calcium in various diseases of infancy and childhood are in progress.

The total serum calcium, as determined in thirty-two cases, averaged 11.4 mg. per hundred cubic centimeters of serum. The average diffusible serum calcium, as estimated in forty-two determinations, was 5.3 mg. or 46.7 per cent. The nondiffusible calcium averaged 6.2 mg., or 53.6 per cent, in thirty-one determinations. No significant statistical correlation could be found between the total or diffusible calcium and the inorganic phosphates, protein fractions, chlorides or cholesterol.

A chart is presented showing the frequency distribution of the total calcium, the diffusible calcium in the serum and the diffusible calcium in the filtrate.

It is suggested that studies of calcium partition are of definite use in the interpretation of any clinical condition involving calcium disturbance.

PNEUMONIA IN CHILDREN

A BACTERIOLOGIC STUDY *

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The designation of the miscellaneous group of pneumococci as type IV has led to considerable misconception as to the real nature of these micro-organisms. It is difficult for those who are not intimate with this classification to realize that the so-called type IV is not a specific type in the sense that the three fixed types are specific, but that it is merely a term used to cover all the remaining strains that do not fall into types I, II or III. It has long been known that type IV pneumococci were amenable to further and more accurate classification; indeed, several observers (Olmstead,[1] Clough [2] and Robinson [3]) have conducted investigations along this line.

In a recently published article, Cooper, Edwards and Rosenstein,[4] who were working in the general investigation of pneumonia under the direction of Dr. Park, have reported ten distinct immunologic types obtained from the group IV pneumococci, which they have designated by Roman numerals from IV to XIII. Since then several additional types have been separated.[5]

Previous bacteriologic studies on pneumonia in children by Wollstein and Benson,[6] Pisek and Pease,[7] Mitchell,[8] Lyon,[9] Wollstein,[10]

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* From the Second (Cornell) Medical Division and the Children's Medical Division (Columbia University, College of Physicians and Surgeons) and the Pathological Department, Bellevue Hospital.

* This work also received important financial aid from the Metropolitan Life Insurance Company's Influenza Commission Fund and from the New York University Commonwealth Pneumonia Fund.

1. Olmstead, M.: Proc. Soc. Exper. Biol. & Med. **14**:29, 1916.

2. Clough, M. C.: Bull. Johns Hopkins Hosp. **28**:306, 1917.

3. Robinson, G. H.: Immunologic Relations of Type IV Pneumococci Obtained During an Epidemic, J. Infect. Dis. **41**:417 (Dec.) 1927.

4. Cooper, G.; Edwards, M., and Rosenstein, C.: J. Exper. Med. **49**:461, 1929.

5. Personal communication from Miss Cooper.

6. Wollstein, M., and Benson, A. W.: Types of Pneumococcus, Am. J. Dis. Child. **12**:254 (Sept.) 1916.

Webster [11] and Westlund [12] have shown a high incidence of cases of group IV pneumococci. These results are shown in table 1. A comparison with those reported in adult cases by Avery, Chickering, Cole and Dochez,[13] Cecil, Baldwin and Larsen,[14] Park, Bullowa and Rosenblüth,[15] and Cecil and Sutliff,[16] and found in table 2 shows a much higher incidence of group IV pneumococci in children. In 614 cases of pneumonia in children, 52.9 per cent showed group IV pneumococci, while in 4,045 cases of lobar pneumonia in adults, only 34.1 per cent are reported as of this group. This observation suggested the importance of making a further bacteriologic study of pneumonia in children, with the purpose of determining the incidence of the ten new types previously included in group IV.

All cases of pneumonia on the Children's Medical Division of Bellevue Hospital were available for this investigation. This service includes all the children under 12 years of age entering the hospital. The patients with acute cases are assigned to two wards, those under 2 years of age to one ward and those over 2 to the other. The work began on Nov. 1, 1928, and ended April 30, 1929.

This study was made possible through the consent and cooperation of Dr. Charles Hendee Smith, director of the Children's Medical Division, and of Dr. William H. Park, director of the Bureau of Laboratories of the Department of Health of New York City, from which laboratories Miss Cooper supplied us with the various diagnostic serums. The diagnosis of bronchopneumonia, lobar or lobular pneumonia was made in each case by following the routine established by Dr. Smith in the clinical study under way at the same time, that is, detailed observation of the clinical course, physical signs and roentgen observations.

7. Pisek, G. R., and Pease, M. C.: Am. J. M. Sc. **151**:14, 1916.

8. Mitchell, A. G.: Penn. M. J. **20**:343, 1917.

9. Lyon, A. B.: Bacteriologic Studies of Pneumonia and Postpneumonic Empyema, Am. J. Dis. Child. **23**:72 (Jan.) 1922.

10. Wollstein, M.: New York State J. Med. **23**:148, 1923.

11. Webster, O. D.: M. J. Australia **1**:129, 1924.

12. Westlund, R. E.: Incidence of Pneumococcus Types in Pneumonia of Children, J. Infect. Dis. **38**:514 (June) 1926.

13. Avery, O. T.; Chickering, H. T.; Cole, R., and Dochez, A. R.: Monograph 7, Rockefeller Inst. M. Research, 1917.

14. Cecil, R. L.; Baldwin, H. S., and Larsen, N. P.: Lobar Pneumonia; Clinical and Bacteriologic Study of 2,000 Typed Cases, Arch. Int. Med. **40**:253 (Sept.) 1927.

15. Park, W. H.; Bullowa, J. G. M., and Rosenblüth, M. B.: Treatment of Lobar Pneumonia with Refined Specific Antibacterial Serum, J. A. M. A. **91**:1504 (Nov. 17) 1928.

16. Cecil, R. L., and Sutliff, W. D.: Treatment of Lobar Pneumonia with Concentrated Antipneumococcus Serum, J. A. M. A. **91**:2035 (Dec. 29) 1928.

TABLE 1.—*Bacteriologic Classification of Pneumonia in Children*

Series Reported	Pneumococci								No Pneumococci		Total
	Type I		Type II		Type III		Unclassified				
	No.	%	No.	%	No.	%	No.	%	No.	%	
Wollstein and Benson, 1916, New York, age under 4½ years											
Lobar pneumonia	3	21.4	2	14.2	0	...	7	50.0	2	14.2	14
Bronchopneumonia	3	8.3	4	11.1	0	...	21	58.2	8	22.2	36
Pisek and Pease, 1916, New York, age under 6 years											
Lobar pneumonia	9	29.0	11	35.5	1	3.2	7	22.6	3	9.7	31
Bronchopneumonia	2	6.3	3	9.4	3	9.4	12	37.4	12	37.4	32
Mitchell, 1917, Philadelphia, mostly under 6 years											
Lobar and bronchopneumonia	10	11.1	10	11.1	3	3.3	67	74.4	0	....	90
Lyon, 1922, Boston, age under 12 years											
Lobar pneumonia	14	19.1	2	2.7	7	9.6	30*	40.4	14	19.2	73
Bronchopneumonia	3	9.7	1	3.2	2	6.4	13*	41.9	12	38.6	31
Wollstein, 1909, New York, age under 3 years											
Lobar and bronchopneumonia	3	3.5	7	8.1	0	...	54	63.1	23	26.8	87
Webster, 1914, Australia, age under 12 years											
Lobar pneumonia	46	38.3	6	5.0	7	5.8	40	40.8	12	10.0	120
Westhaud, 1920, Chicago, age under 12 years											
Lobar pneumonia	4	5.7	12	17.2	2	2.9	42	60.8	9	13.0	69
Bronchopneumonia	2	5.8	3	8.8	1	2.9	18	52.6	10	29.4	34
Total	99	16.1	61	9.9	26	4.2	326	52.9	105	17.1	614

* This includes one case which is classified as type IIa by Lyon.

TABLE 2.—*Bacteriologic Classification of Lobar Pneumonia in Adults*

Series Reported	Pneumococci								Total
	Type I		Type II		Type III		Unclassified		
	No.	%	No.	%	No.	%	No.	%	
Avery, Chickering, Cole and Dochez, 1917, New York	151	33.3	131	29.3	59	13.0	111*	24.5	454
Cecil, Larsen and Baldwin, 1927, New York	644	33.6	368	19.1	268	13.3	633	33.1	1,913
Park, Bullowa and Rosenbluth, 1918, New York	293	38.5	124	15.6	85	10.6	201	45.5	793
Cecil and Sutliff, 1928, New York	300	33.9	214	24.2	96	10.8	275	31.1	885
Total	1,388	32.6	839	20.7	508	12.0	1,080	24.1	4,045

* This includes 19 cases which are classified as type IIa by Avery, Chickering, Cole and Dochez.

METHOD

The routine typing was done from throat swabs, of which one or more were obtained from each patient. The pharynx was streaked several times or until the patient coughed. Sometimes, a specimen of thick, tenacious sputum, occasionally rusty, was seen to adhere to the swab. The swab was put into 3 cc. of beef-heart-infusion broth, p_H 7.8, and sent to the laboratory. One or more blood cultures were taken on all patients, except those who were convalescent on admission. The method used was to withdraw 3 cc. of blood; 1 cc. was put into 9 cc. of broth, and 1 cc. was used for each of two agar pour plates. Specimens of sputum, ear exudate or chest fluid which were obtained whenever possible, exudate from postmortem punctures of the lung and lung tissue obtained at autopsy were sent to the laboratory for culture.

In the laboratory, a number of preliminary experiments were carried out to determine the quickest and most accurate method of finding the infecting organism in the various specimens received. Plain broth was found to be better than blood broth for the swab cultures. More rapid results were obtained when the swab culture was incubated for several hours before inoculation into the mouse. The simple plate method as described by Wollstein,[6] in which a drop of the inoculated broth is streaked on a plate and, after incubation, cultures from the individual colonies of pneumococci typed, was compared with the mouse method. In several instances, pneumococci were obtained by the mouse method, when no pneumococci could be isolated from the plate.

The procedure decided on for isolating the organisms from the swab culture was a combination of the plate and mouse methods, and paralleled closely the methods used by Westlund.[7,8]

A blood agar plate was streaked from the broth culture immediately on being brought to the laboratory. The culture was then incubated at 37 C. for three hours, and 1 cc. was inoculated intraperitoneally into a white mouse. The mouse was allowed to die and autopsy was performed. Cultures from the peritoneal exudate and heart's blood were streaked on blood agar plates. Agglutination and precipitation tests were made on the peritoneal exudate with the diagnostic serum supplied by the New York City Department of Health. A final confirmation was made by agglutination tests on broth cultures grown from discreet colonies from the heart's blood and by testing these organisms for bile solubility. In a few cases a type was obtained from the heart's blood which was different from that from the peritoneal exudate, indicating a mixed infection in the mouse. Occasionally a type was procured from the heart's blood when none had been obtained from the exudate, and vice versa.

Whenever the mouse did not die within several days, or when a fixed type of pneumococcus was not procured from the peritoneal exudate or the heart's blood, a fresh swab was taken from the throat and the foregoing procedure was repeated. If the mouse did not die within fifteen days, it was killed and the peritoneal fluid and heart's blood streaked on a blood agar plate. In one case, a fixed type of pneumococcus was recovered in this way.

The blood plates streaked from the swab culture were examined in every case and the predominance of an organism noted. If pneumococci were not obtained by the mouse method but were found on the plate, broth cultures were made from several individual colonies, and the cultures typed.

Specimens of sputum and chest fluid were inoculated into mice, and the peritoneal exudate and heart's blood were studied as already noted. In each case, a smear of the exudate was made, stained and examined microscopically. The

chest fluids as well as the eye and ear cultures were streaked directly on blood agar plates, and the individual colonies isolated and studied.

As a control series, three distinct types of cases were used: (1) cases of infection of the upper respiratory tract occurring in the wards with the pneumonia patients; (2) cases in which the patients had no signs of infection of the respiratory tract but were exposed to pneumonia in the wards; and (3) cases in which the patients had no signs of respiratory disease and were not exposed in the hospital.

TABLE 3.—*Comparison of Bacteriologic Observations Obtained from Throat Swab with Those Obtained from Other Sources*

Swab	Chest Fluid	Blood Culture	Postmortem Culture	Sputum	Ear
Type I	Type I				
Type I	Type I				
Type I,* uncl.	Staph. aur.				
Type I, uncl.	Type I				
Uncl.*	Type I				Type I
Type V	Type V	Type V	Type V		
Type VI	Type VI				
Type VI,* uncl.	Type IX				
Uncl., Strep. hem.	Uncl.				
Uncl.	Uncl.				
Type IV, uncl.		Type IV Staph. aur.			
Type VII		Type VII	Type VII		
Uncl.*		Staph. aur.	Staph. aur.		
Uncl.		Uncl.			
Strep. hem., uncl.		Uncl.		Strep hem.	
Type I*			Strep. hem.		
Type III			Type III		
Type VI			Type VI		
Uncl.			Uncl.		Uncl.
Uncl.			Uncl.		
Uncl.			Uncl., Staph. aur.		
Strep. hem.			Strep. hem.		
Type I, uncl.				Type I	
Type V				Type V	
Type V				Type V	Type V
Type VIII				Type VIII	
Uncl.				Uncl.	
Uncl., type VI				Uncl., type VI	Uncl.
Uncl.				Uncl.	
Type III					Type III
Type IV, XIII, uncl., strep. hem.					Uncl., strep. hem.
Uncl.					Uncl., Staph. aur.
Uncl.					Uncl., Staph. aur.
Uncl., Strep. hem.					Strep. hem.
Uncl.					Uncl.
Uncl., Strep. hem.					Uncl., Staph. aur.
Uncl.*					Type VII

* Not corroborated by other specimens.

Swabs from the throat were obtained and the same bacteriologic procedures were employed as in the cases of pneumonia.

RESULTS

In 37 of the 147 cases included in this series, checks on the swab method were obtained by cultures from the sputum, blood, ear exudate or chest fluid or from specimens procured by postmortem puncture of the lung or at autopsy. These checks are to be found in table 3. In 31, or 84 per cent, of the cases, the organism obtained from the throat swab and considered the causative agent of the pneumonia was

corroborated by a culture from some other body fluid or exudate. Identical observations were not obtained in 6 cases. Three of these discrepancies occurred in what appeared to be type I infection, and 1 of the 3 showed type I pneumococcus in the swab and *Staphylococcus aureus* in the chest fluid. Possibly the staphylococcus was a contamination from the skin or the atmosphere. Only 2 cases suggested a failure of the swab method. In 1 of these an unclassified pneumococcus was reported from the swab culture, and type I pneumococcus was found in the chest fluid and ear exudate. The other showed a type VI

TABLE 4.—*Bacteriologic Classification of Pneumonia in Children, Bellevue Hospital, Nov. 1, 1928-April 30, 1929*

	Number of Cases	Percentage Incidence
Type I	14	9.5
Type II	3	2.0
Type III	3	2.0
All other pneumococci	120	81.6
No pneumococci	7	4.8
Total	147	

TABLE 5.—*Incidence of Types of Pneumonia in Children, Bellevue Hospital, Nov. 1, 1928-April 30, 1929*

	Number of Cases	Percentage Incidence
Type I	14	9.5
Type II	3	2.0
Type III	3	2.0
Type IV	4	2.7
Type V	9	6.1
Type VI	19	12.9
Type VII	5	3.4
Type VIII	1	0.7
Type IX	6	4.1
Types X, XI, XII and XIII	3	2.0
Unclassified	73	49.7
No pneumococci	7	4.8
Total	147	

pneumococcus in the swab and a type IX pneumococcus in the chest fluid. In these cases, moreover, the possibility of a mixed infection must not be overlooked.

In 1 case of type I pneumonia, in addition to obtaining the type I organism from the ear exudate and the chest fluid, a positive precipitin test on the urine was made. Another patient with an unclassified pneumococcus pneumonia had a severe conjunctivitis, and a culture from the conjunctival sac showed unclassified pneumococci.

Incidence of Types.—Table 4 was prepared in order to make a direct comparison of our Bellevue series with those of other investigators, as shown in tables 1 and 2. Our children's series attributed 81.6 per cent of the cases to the unclassified pneumococci as compared with 52.9 per

cent in the composite table (table 1). Part of this difference is accounted for by the low incidence of pneumonia due to *Streptococcus hemolyticus* (grouped in the tables under "no pneumococci"), and this, no doubt, was partly due to the fact that there was little scarlet fever and measles in New York during the year of this investigation, and the cases of streptococcus pneumonia which frequently complicate these diseases were few.

Table 5 shows that group IV is reduced from 81.6 to 49.7 per cent by including the ten new types of Cooper, Edwards and Rosenstein.[4] Type VI is found more frequently than type I, and types IV, V, VI, VII and IX occur more often than either type II or type III.

TABLE 6.—*Control Cases to Show Incidence of Types of Pneumococci in Children Not Having Pneumonia*

Organism	Series I	Series II	Series III	Total	Percentage Incidence
Pn. I	0	1	0	1	0.6
Pn. II	0	0	0	0	0.0
Pn. III	4	2	2	8	5.0
Pn. IV	1	2	1	4	2.5
Pn. V	3	0	0	3	1.9
Pn. VI	9	4	1	14	8.7
Pn. VII	2	1	0	3	1.9
Pn. VIII	3	1	1	5	3.1
Pn. IX	2	0	1	3	1.9
Pn. X	0	0	0	0	0.0
Pn. XI	1	0	1	2	1.2
Pn. XII	0	0	0	0	0.0
Pn. XIII	1	0	2	3	1.9
Pn. unclassified	34	19	18	71	44.1
No pneumococci	12	16	16	44	27.3
Total	72	46	43	161	

Series I: Cases of infection of upper respiratory tract occurring on the wards with pneumonia patients.
Series II: Cases in which patients had no signs of respiratory infection but were exposed to pneumonia in the wards.
Series III: Cases in which patients had no signs of respiratory disease and were not exposed in the hospital.

Control Cases.—One hundred and sixty-one control cases in children are shown in table 6. They are grouped in three series: (1) cases of infection of the upper respiratory tract occurring on the wards with the pneumonia patients, (2) cases in which the patients had no signs of respiratory infection but were exposed to pneumonia in the wards, and (3) cases in which the patients had no signs of respiratory disease and were not exposed in the hospital. Pneumococci, particularly those of the fixed (classified) types, were found more frequently in the cases of patients with respiratory infection. Seventy-three per cent of the 161 patients carried pneumococci; 29 per cent carried fixed types, and 44 per cent carried unclassified strains. Type I pneumococcus was isolated in one case only. Type III pneumococcus, which Avery, Chickering, Cole and Dochez [18] found in the throats of 28 per cent of a series of normal adults, was found in only 5 per cent of the cases in our series. Type VI, the most common type in the series of cases of pneumonia in children,

was also most frequently found in the controls, being isolated from 9 per cent of the cases.

Incidence of Types According to Age.—Table 7 divides the 147 cases in the pneumonia series into age groups: 53 occurred in children under 1 year of age; 36, in those from 1 to 3 years; and 58, in patients from 3 to 12 years. It is found that 53 cases occurred in the first year; an average of 18 per year, in the second and third years; and an average of 6 per year, from the third to the twelfth year. This shows a much higher incidence of pneumonia in children under 1 year, and a gradual drop in the incidence curve thereafter. Eleven of the 14 patients with type I pneumonia were in the group of children from 3 to 12 years of age, and all 9 of the type V cases occurred in the same group. The type VI and the unclassified pneumococcus pneumonia had an age distribution similar to that of the entire series. The remaining types did

TABLE 7.—*Incidence of Types of Pneumonia in Children According to Age*

	Total Cases	Under 1 Year		1 to 3 Years		3 to 12 Years	
		Cases	Deaths	Cases	Deaths	Cases	Deaths
Type I	14	3	1	0	0	11	0
Type II	3	0	0	1	0	2	0
Type III	3	3	1	0	0	0	0
Type IV	4	1	1	2	0	1	0
Type V	9	0	0	0	0	9	1
Type VI	19	7	1	7	1	5	1
Type VII	5	3	1	0	0	2	0
Type IX	6	4	1	2	0	0	0
Types VIII, X, XI, XII and XIII	4	2	2	1	0	1	0
Unclassified	73	26	9	22	1	25	2
No pneumococci	7	4	5	1	0	2	0
Total	147	53	20	36	2	58	4

not include a sufficient number of cases to be of value in determining the general distribution according to age.

Incidence of Types According to Clinical Diagnosis.—There were 147 cases of pneumonia in the series: 103 of lobar pneumonia, 29 of bronchopneumonia, 6 of lobular pneumonia, 2 of lobar with terminal bronchopneumonia and 7 in which the clinical variety could not be determined. The fixed types except types III and VI were more frequently found in cases of lobar pneumonia. Thirty-six of the 41 cases of pneumonia caused by types I, II, IV, V, VII and IX were of the lobar variety. Eight of the 19 cases of type VI infection were of the broncho type, and 2 were of the lobular. Of the 3 type III cases, 1 was bronchopneumonia and the other 2 were atypical, and could not be included in any of the clinical types. The unclassified pneumococcus pneumonias showed a distribution corresponding to that of the total series.

The foregoing analysis seems to indicate that certain types of pneumococci are prone to induce lobar pneumonia, while other types are

associated with bronchopneumonia. This, however, is probably misleading, for if other important factors are considered, the cases studied form too small a group to make the results conclusive.

Mortality Rate.—Table 4 shows a mortality rate of 17.7 per cent for the 147 cases in the series. The type VI and unclassified groups show almost the same rate, while in the 14 cases of type I, only 1 death

TABLE 8.—*Incidence of Types in Children According to Clinical Diagnosis*

	Number of Cases	Lobar Pneumonia	Broncho-pneumonia	Lobular Pneumonia	Miscellaneous*
Type I	14	13	1	..	..
Type II	3	3	..	..	..
Type III	3	..	1	..	2
Type IV	4	4	..	..	..
Type V	9	8	..	..	1
Type VI	19	9	8	2	..
Type VII	5	2	3	..	..
Type IX	6	6	..	..	..
Types VIII, X, XI, XII and XIII	4	1	2	..	1
Unclassified	73	52	13	4	4
No pneumococci	7	5	1	..	1
Total	147	106	29	6	9

* This group includes two cases of lobar pneumonia with a terminal bronchopneumonia and seven cases of pneumonia in which the clinical type could not be determined.

TABLE 9.—*Death Rate According to Type of Pneumonia in Children, Bellevue Hospital, Nov. 1, 1928-April 30, 1929*

	Number of Cases	Number of Deaths	Mortality Rate
Type I	14	1	7.1
Type II	3	0	0.0
Type III	3	1	33.3
Type IV	4	1	25.0
Type V	9	1	11.1
Type VI	19	3	15.8
Type VII	5	1	20.0
Type VIII	1	0	0.0
Type IX	6	1	16.7
Types X, XI, XII and XIII	3	2	66.7
Unclassified	73	12	16.4
No pneumococci	7	3	42.9
Total	147	26	17.7

occurred, making a low rate. In the other groups, the number of cases is too small for the figures to be significant.

Complications.—The complications encountered were otitis media, empyema, bacteremia and nephritis. Pneumococcus meningitis was not recognized in any of these cases. The complications, particularly otitis media, seemed to occur more frequently in pneumonia caused by the fixed types of pneumococci. Twenty of the 24 cases of otitis media were found in the fixed types, and only 2, in the unclassified group; in 11 of the 24 cases, the same organism was isolated from the ear exudate as was obtained from the throat swab.

In table 10 it is seen that empyema occurred in 11 cases, all of which were lobar pneumonia, and 8 were pneumonias caused by fixed types. In two of 73 cases of unclassified pneumococcus pneumonia empyema developed, while 5 of 14 cases of type I were followed by this complication. Six of the 11 patients with empyema died. All of the patients with empyema following type I recovered. The high incidence of empyema in type I has been pointed out by Cecil, Baldwin and Larsen, and by several investigators of pneumonia in children. Lyon [9] cultured type I pneumococcus from 11 of 15 cases of empyema following pneumonia. Webster [11] attributed 19 of 55 cases of empyema to type I pneumococcus. Mitchell,[8] however, encountered 6 cases of empyema in his series, and all of these were attributed to the unclassified pneumococci.

TABLE 10.—*Occurrence of Empyema and Otitis Media in the Different Types of Pneumonia in Children*

	Total Cases	Empyema	Otitis Media
Type I	14	5	5
Type II	3	0	0
Type III	3	0	3
Type IV	4	0	3
Type V	0	1	1
Type VI	10	1	3
Type VII	5	0	3
Type IX	6	1	2
Types VIII, X, XI, XII and XIII	4	0	1
Unclassified	73	3	2
No pneumococci	7	1	2
Total	147	11	24

Bacteremia was discovered in 6 of the 147 patients. There were 118 blood cultures taken on 99 of the cases. Whenever the condition of the patient was serious enough to suggest that a blood culture might be positive, one was taken. Six of 99 patients, or 6.1 per cent, had positive blood cultures, and if there were only 6 in the 147, which is probable, the percentage would have been 4.1. Three of these 6 patients died and 3 recovered. The 3 that recovered followed cases of unclassified pneumococcus pneumonia, and of the 3 that died, there was one each of types IV, V and VII infection. Bacteremia is less frequently a complication in the pneumonia of children than in that of adults. Wollstein,[10] in 11 cases of lobar pneumonia in children, obtained one positive blood culture. Lyon [9] took blood cultures in 43 of 73 cases of lobar pneumonia and reported 6, or 14 per cent, positive. In 11 of 31 cases of bronchopneumonia he found 3 positive. Cecil [17] stated that one third of all cases of lobar pneumonia in adults show a positive blood culture.

17. Cecil, R. L.: A Textbook of Medicine, Philadelphia, W. B. Saunders Company, 1927.

Acute nephritis occurred during the course of the pneumonia in 4 of the 147 cases, once in type VI and three times in the unclassified group. The occurrence of nephritis in pneumonia of children is not as uncommon as in that of adults.

Mixed Infections.—In 38 of the 147 cases, the bacteriologic studies showed more than one organism. In about one half of these cases, the first swab revealed only unclassified pneumococci, while later control swabs showed fixed types. In most of these cases, the pneumonia, except when the unclassified organism was checked by one from the chest fluid or some other body fluid, was thought to be caused by the fixed type. In all cases, a blood plate was streaked and carefully studied, and the predominance of organisms other than pneumococci was reported. In 9 cases, an unclassified pneumococcus killed the mouse and was obtained from the exudate. In these, however, a blood agar plate, streaked from the swab culture, showed a predominance of *Streptococcus hemolyticus*. Whether the pneumonia in these cases was caused by pneumococcus, streptococcus or both cannot be decided. In the present series these cases are grouped as unclassified pneumococcal infections. This point can well be disputed. A case is classified as a streptococcus hemolyticus pneumonia: (*a*) when the organism is found in the chest fluid or blood, (*b*) when it comes through the mouse and is found on the blood agar plate, or (*c*) when it predominates on the blood agar plate and the mouse cultures are sterile. Only one case in our series satisfied this criterion. In 6 cases no pneumococci came through the mouse or were found on the blood agar plates—*Staphylococcus aureus*, *Streptococcus viridans* or the influenza bacillus predominated. These cases, including one of the streptococcus hemolyticus, are reported in our tables under the heading of "No Pneumococci."

SUMMARY AND CONCLUSIONS

1. A review of the literature shows a much higher incidence of group IV, or unclassified pneumococcus, pneumonia in children than in adults. The recent report of Cooper, Edwards and Rosenstein [4] suggests the possibility of reducing this unclassified group by the identification of their ten new fixed types.

2. The cases of all patients with pneumonia admitted to the Children's Medical Division of Bellevue Hospital from Nov. 1, 1928, to April 30, 1929, were studied clinically and bacteriologically. One hundred and forty-seven cases are included in this series, and the ward procedures and laboratory methods employed are presented in this report.

3. A control series of 161 children was studied at the same time and by the same bacteriologic methods.

4. The accuracy of the throat swab method of typing is shown by a series of 37 cases in which cultures were obtained from the sputum, blood, ear exudate, chest fluid or specimens procured by postmortem puncture of the lung or at autopsy.

5. The unclassified group in the 147 cases of pneumonia was reduced from 81.6 to 49.7 per cent by the separation of the ten new types of Cooper, Edwards and Rosenstein.[4] The incidence of types in the 147 cases of pneumonia in children is tabulated.

6. The incidence of types in the 161 control children, 72 of whom had respiratory infections but not pneumonia, is tabulated; 73 per cent had pneumococci in the throat; 29 per cent had one of the fixed types, and 44 per cent had unclassified strains.

7. The incidence of types according to age is recorded. The incidence of pneumonia in general is high in the first year and drops rapidly after that. A higher incidence of the fixed types was found after the first year.

8. The cases are classified according to clinical diagnosis. The tables show a predominance of types I, II, IV, V, VII and IX in the cases of lobar pneumonia and a high incidence of type VI in the cases of bronchopneumonia. For reasons pointed out, no conclusions as to relationship between type and kind of pneumonia can be estimated.

9. The mortality rate in the 147 cases of our series is 17.7 per cent, and the variation according to type is reported.

10. The complications, including otitis media, empyema, bacteremia and nephritis are listed, and variations with the types are pointed out.

11. Up to the present time, the number of cases of the new types studied has been so small that accurate conclusions as to their prognosis and clinical course cannot be presented.

NITRITE REACTION AS A DIAGNOSTIC TEST IN INFLUENZAL MENINGITIS *

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The ability of *B. influenzae* to reduce nitrates to nitrites may be used as a rapid diagnostic test in influenzal meningitis. The organisms which commonly cause meningitis, such as meningococci, tubercle bacilli and streptococci, are not nitrate reducers. Staphylococci and various members of the colon-typhoid group, though nitrate reducers, rarely cause meningitis, and are easily differentiated from the influenza bacillus, the most frequent cause of meningitis among the nitrate-reducing bacteria.

Rivers [1] found nitrate reduction in fifteen meningitic and eighteen respiratory strains of *B. influenzae*. Jordan and Reith [2] tested 287 strains of *B. influenzae* of the respiratory type and found that every one reduced nitrates to nitrites. They regarded nitrate reduction as an important differential criterion for this organism.

Rivers [3] proposed a direct indol test on the spinal fluid for the rapid diagnosis of influenzal meningitis, based on Jordan's [4] observations that most strains of *B. influenzae* produced indol. Rivers did not report testing the spinal fluids in influenzal meningitis for nitrate reduction.

During the past five years I have applied the nitrite reaction to the spinal fluids sent to the laboratory of the Milwaukee Children's Hospital and have found this reaction negative in meningococcic, streptococcic and tuberculous meningitis. A positive nitrite reaction was obtained in thirteen consecutive cases of influenzal meningitis. No patients with staphylococcic or colon meningitis were observed during this time.

METHOD

The first nitrite tests were performed with the standard alpha-naphthyl-amine-sulphanilic acid reagent, but this reagent gave a slight positive reaction with normal spinal fluids and therefore was discarded as

* Submitted for publication, March 20, 1930.

1. Rivers, T. M.: Influenzal Meningitis, Am. J. Dis. Child. **24**:102 (Aug.) 1922.

2. Jordan, E. O., and Reith, A. F.: Studies on Respiratory Diseases, J. Infect. Dis. **34**:239 (March) 1924.

3. Rivers, T. M.: Indol Test on Spinal Fluid for Rapid Diagnosis of Influenzal Meningitis, J. A. M. A. **75**:1495 (Nov. 27) 1920.

4. Jordan, E. O.: Production of Indol by Certain Strains of Pfeiffer Bacillus, J. A. M. A. **72**:1542 (May 24) 1919.

being too sensitive. Dimethyl-alpha-naphthyl-amine, as proposed by Wallace and Neave,[5] was substituted for alpha-naphthyl-amine in the reagent. This reagent is not as sensitive, but it still gave slight positive reactions with normal control spinal fluids. Finally, the old starch-iodide test of Fresenius was tried. This was found to be quite satisfactory and gave negative reactions with normal spinal fluids.

The test was simple. A few crystals of nitrite-free sodium nitrate were added to a tube of freshly withdrawn spinal fluid. The spinal fluid was incubated for from four to eight hours, and was then ready for the test. First, a few drops of diluted sulphuric acid were added, then, a few drops of diluted potassium iodide solution and then 2 or 3 cc. of starch paste. If nitrites were present, a deep blue color appeared, due to the formation of free iodine by the nitrous acid. A positive nitrite test could often be obtained early in influenzal meningitis without incubating the spinal fluid with sodium nitrate crystals, but in the later stages of the disease, it was necessary to add sodium nitrate so that a sufficient quantity of nitrate was available for reduction to nitrite.

As an illustration of the diagnostic value of this reaction, the following case may be cited. A patient with pertussis and complicating pneumonia developed meningeal symptoms. The spinal fluid contained gram-negative bacilli. The question arose as to whether these organisms were *B. influenzae* or *B. pertussis*, as they are closely related morphologically. The nitrite reaction with the spinal fluid was positive. *B. pertussis* does not reduce nitrates to nitrites. Further cultural studies of the organism showed it to be *B. influenzae*, which was suggested by the nitrite test. A positive nitrite reaction may be obtained very quickly. In one case, it was strongly positive one hour after the spinal fluid was incubated.

SUMMARY

A positive nitrite reaction with the spinal fluid was obtained in thirteen consecutive cases of influenzal meningitis, and was always absent in meningococcic, tuberculous and streptococcic meningitis. The nitrite test, according to the method described, may be used as a rapid corroborative test for the diagnosis of influenzal meningitis.

5. Wallace, G. I., and Neave, S. L.: J. Bact. 14:377, 1927.

Case Reports

CONGENITAL ATRESIA OF THE BILE DUCTS *

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AND
I. HARRISON TUMPEER, M.D.
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Congenital atresia of the bile ducts is sufficiently rare to warrant presentation of an additional case. Isolated cases have been reported since 1801, but it was not until 1892 that a complete summary of the subject was given by Thomson,[1] who added one case to forty-nine cases that he gathered from the literature. In 1901, Rolleston and Hayne [2] collected ten more cases. Lavenson [3] added one case in 1908, and by 1911, Howard and Wolbach [4] found fourteen additional cases. Since then cases have been reported by Moschovitz,[5] Alfred Hess,[6] Holmes,[7] Feldman,[8] Hauser,[9] Vigholt,[10] Rosenberg and Judd [11] and others.

For a clear understanding of this anomaly, it may be well to recall briefly the development of the biliary system.[12] At about the third week of intra-uterine existence a longitudinal groove appears on the ventral wall of the duodenum. On the external surface of the intestine this groove appears as a projection which rapidly increases in size and grows forward and upward toward the lower part of the septum transversum. This groove is a mass of mesodermic tissue lying in front of the foregut and conveys the umbilical and vitelline veins. At an early stage a cranial

* Submitted for publication, March 7, 1930.

* From the Sarah Morris Hospital for Children of the Michael Reese Hospital.

1. Thomson: Edinburgh M. J. **37**:606, 1892.

2. Rolleston and Hayne: Brit. M. J. **2**:947, 1901.

3. Lavenson: J. M. Research **18**:161, 1908.

4. Howard, C. P., and Wolbach, S. B.: Congenital Obliteration of the Bile-Ducts, Arch. Int. Med. **8**:557 (Nov.) 1911.

5. Moschovitz: Proc. New York Path. Soc. **12**:41, 1912-1913.

6. Hess, Alfred F.: A Consideration of the Pancreas and Its Ducts in Congenital Obliteration of the Bile Ducts, Arch. Int. Med. **10**:37 (July) 1912.

7. Holmes, James B.: Congenital Obliteration of the Bile-Ducts, Am. J. Dis. Child. **11**:405 (June) 1916.

8. Feldman, W. M.: Brit. J. Dis. Child. **22**:215, 1925.

9. Hauser: Hospitalstid. **69**:77, 1926.

10. Vigholt, W.: Acta obst. et gynec. Scandinav. **7**:146, 1928.

11. Rosenberg, Lester, and Judd, George E.: Congenital Atresia of the Bile Ducts, Arch. Surg. **18**:2339 (April) 1929.

12. Hertwig: Elemente des Entwicklungslehre, ed. 5, Jena, Gustav Fischer, 1915.

portion (pars hepatica) and a caudal portion (pars cystica) can be differentiated in this liver bud (fig. 1). The pars hepatica sends out trabeculae which come in contact with the blood vessels in the septum and enclose them. The trabeculae become hollowed out and reduced in size by branching so that finally a minute channel, representing a bile capillary, remains in the center. The bile capillaries of adjacent trabeculae converge and unite, forming the intrahepatic bile ducts. These ducts unite to form the hepatic ducts. Yippo [13] stated that they are at first patent but later lose their lumina by epithelial proliferation only to become canalized later. This process is similar to that which takes place in other parts of the intestinal tract. The liver separates from the duodenum as it grows, maintaining connection to it only by a stalk which represents the future common duct. The pars cystica remains

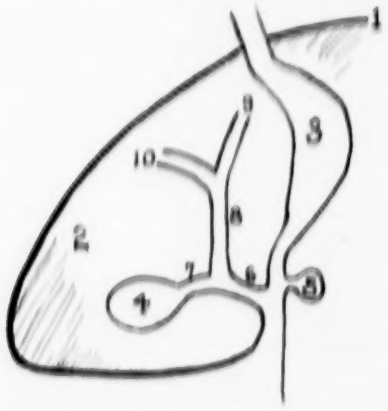

Fig. 1.—Diagram of the development of the bile tracts. 1 indicates the diaphragm; 2, ventral mesentery; 3, stomach; 4, gallbladder; 5, dorsal pancreas bud; 6, original liver bud, common duct; 7, caudal portion of common hepatic duct (cystic duct); 8, cephalic portion of common hepatic duct; 9, left hepatic duct; 10, right hepatic duct.

hollow and becomes the gallbladder. It becomes constricted off from the duct, and the constriction forms the future cystic duct.

From the complexity of development it can be seen that many anomalies of the biliary system are possible, and of these atresia of the bile passages forms only a small percentage. With improved technic of biliary surgical procedures, other anomalies have been brought to view by Eisendrath,[14] Mentzer,[15] Emanuel Friend [16] and others. These con-

13. Yippo: Ztschr. f. Kinderh. **9**:319, 1913.

14. Eisendrath, D. N.: Boston M. & S. J. **182**:573, 1920.

15. Mentzer, S. H.: Anomalous Bile Ducts in Man, J. A. M. A. **93**:1273 (Oct. 26) 1929.

16. Friend, Emanuel: Illinois M. J. **56**:169, 1929.

sist largely in anomalous positions of biliary passages with relation to each other and nearby structures. In a series of autopsies, Eisendrath reported the frequent finding of: (*a*) anomalous course and union of cystic and hepatic ducts, (*b*) accessory small hepatic duct in 12 per cent of bodies and (*c*) anomalous origin and course of the cystic and hepatic arteries in about 10 per cent of the bodies examined. If one limits oneself to atresias, many variations may be found even in these cases. For instance, Parsons and Hickmans [17] described a case of a complete atresia of the intrahepatic but not the extrahepatic ducts. Complete absence of the gallbladder and extrahepatic ducts has been described by Hill,[18] and absence of the gallbladder with the common duct dilated to form the so-called choledochus cyst was reported by Ishiama.[19] In about 16 per cent of the cases of atresia of the common duct, the cystic and hepatic ducts are normal.

REPORT OF CASE

History.—M. R. was first seen at the age of 7 weeks by one of us (A. M.) on June 20, 1929, at an Infant Welfare Station for feeding correction. The infant was markedly jaundiced. The mother had been advised that the condition the infant presented was a normal phenomenon, and that the jaundice would clear up. Additional history indicated that the baby was the result of the first pregnancy. The labor was difficult, lasting seventeen hours, and delivery was effected by forceps. The infant cried immediately after birth and was cyanosed for the first day only. The birth weight was 7 pounds 11 ounces (361.15 Gm.) and the length, 19½ inches (49.53 cm.). There were no convulsions after birth. There were no similar cases of jaundice in the family. The mother said that her physician had noted jaundice at birth, but she noticed it first on the third day. The child was completely breast-fed for the first five weeks and was gaining in weight. Later complementary feedings of cow's milk and carbohydrate were given. The infant retained its food well and was thriving. The stools were greenish for the first six days, but since then had been completely colorless, bulky and greasy. The jaundice had been gradually increasing. The urine had always been dark yellow and stained the diapers. On the basis of the picture of complete biliary obstruction, a negative family history and absence of elevated temperature and signs of syphilis, we concluded that this was a case of congenital anomaly of the bile duct, probably atresia. Hospitalization was advised but was delayed because the parents sought other medical opinions, which did not always agree with ours. The baby was finally admitted to the Sarah Morris Hospital on July 2, at the age of 9 weeks, with a tentative diagnosis of congenital obliteration of the bile ducts.

Examination.—On admittance to the hospital, the infant appeared well nourished, weighing 11 pounds and 3 ounces (4,989.6 Gm.). The temperature was 99.2 F. (rectal). Jaundice was marked, and the sclerae were yellow. There was no lymphadenitis. The chest was normal except for moderate beading of the ribs. The abdomen was slightly protuberant. The liver was palpable two finger-

17. Parsons, L. G., and Hickmans, E. M.: Biliary Cirrhosis, Am. J. Dis. Child. **31**:459 (April) 1926.

18. Hill, N. H.: Lancet **2**:654, 1927.

19. Ishiama: Arch. f. klin. Chir. **151**:183, 1927.

breadths below the right costal margin, and the edge of the spleen was just palpable. An umbilical hernia was present. The mucous membranes were discolored.

Laboratory Examination.—The stools were colorless and greasy during the entire stay in the hospital. On the day of admittance, one stool was yellowish. No blood was noted in any of the stools. Chemical examination revealed the absence of bile pigments. The urine was very dark, staining the diapers greenish yellow. Chemical examination revealed the presence of bile salts, but no urobilin or other pathologic observations.

Examination of the blood showed: hemoglobin, 65 per cent; red cells, 3,110,000; white cells, 16,600; lymphocytes, 70 per cent; polymorphonuclears, 25 per cent; transitionals, 4 per cent; eosinophils, 1 per cent. The coagulation time was three minutes and fifty seconds. The bleeding time was two minutes and forty-five seconds. The fragility test showed: partial hemolysis, 0.38 per cent; normal, 0.42; complete hemolysis, 0.28 per cent, normal 0.32, indicating a somewhat increased resistance to hemolysis.

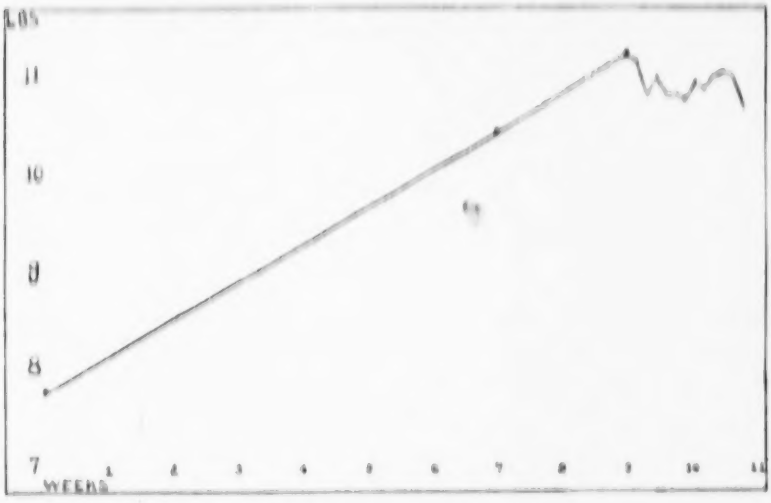

Fig. 2.—Weight curve of M. R.

The icterus index was 120. The calcium was 11.2 mg. per hundred cubic centimeters.

Both the direct and the indirect van den Bergh tests were positive (biphasic). The Wassermann and Kahn tests and the Pirquet test gave negative results.

Roentgen examination revealed no evidence of stones in the region of the biliary structures.

While the infant was in the hospital, on a diet of breast milk complemented by a formula of cow's milk containing 6 per cent added carbohydrates, the weight curve dropped slightly before death (fig. 2).

Operation.—Basing our conclusion on the foregoing observations and course, we advised exploratory laporatomy with the hope that the anomaly might be amenable to surgical drainage of the bile. The operation was performed on July 15, by Dr. Heliodor Schiller, whose observations were as follows: With the infant under ether anesthesia, a midline supra-umbilical incision was made. The liver was markedly enlarged and appeared icteric, and the surface was granular. The

gallbladder was empty. The cystic duct was carefully dissected and was found to terminate in a fibrous band that was attached to the duodenum. The structures at the hilus of the liver were carefully dissected into the hilus. The duct terminated at the hilus as a bulbous structure. It was identified and carefully prepared. It was not patent. No further procedures were advisable, so the incision was closed.

Course.—The following day the infant began to vomit. The temperature, which had varied from 98 to 99.8 F., rose to 104.6 F., and the abdomen was distended. The patient died on July 17, the second day after the operation.

Necropsy.—Necropsy, performed on July 17 by Dr. Otto Saphir, revealed the following observations: The body was that of a well developed white male infant. The skin was bright yellow. The head, lungs and spleen were normal. The kidneys were enlarged and greenish and contained deposits of uric acid crystals in the region of the tips of the pyramids. The liver was large and greenish. On section

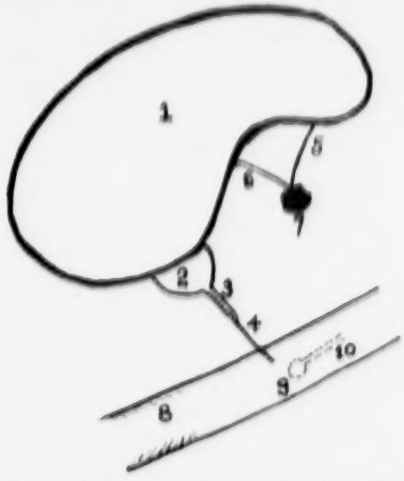

Fig. 3.—Diagram of specimen. 1 indicates the liver; 2, gallbladder; 3, cystic duct (patent); 4, cystic duct (atretic); 5, hepatic duct (left); 6, hepatic duct (right); 7, button-like fibrotic tissue representing common hepatic duct; 8, duodenum; 9, ampula duodenalis (patent); 10, pancreatic duct (patent).

the architecture could be clearly determined in some portions, while in others the structure was obscured. Some parts showed an apparently new formation of lobules, which were bright yellow and elevated. The hepatic ductuli were apparently fibrosed. The gallbladder was present and contained a small amount of stringy, colorless liquid. The cystic duct was present. Its proximal portion was patent, but the distal portion was completely fibrosed. The common duct was absent. Both the right and the left hepatic ducts could be recognized. They were smaller than normal and were apparently fibrosed. In the region of the union of the right and left hepatic duct there was a small button-like mass of fibrosed tissue which ended blindly (fig. 3). The portal vein was normal. The left branch of the hepatic artery was thrombosed. The papilla of Vater and the pancreatic ducts were patent. Microscopic examination revealed necrosis of the liver cells in some portions. In some sections there was a marked new formation of connective tissue encircling the acini. This connective tissue was richly infiltrated

with lymphocytes and endothelial cells. The periportal spaces contained newly formed bile canaliculi (fig. 4). An abundant amount of golden brown pigment could be distinguished.

THEORIES OF DEVELOPMENT

According to Thomson, there is a developmental aplasia, which consists of a narrowness of the lumen of the ducts. Interference with the outflow of bile causes catarrh, blocking and ultimately obliteration due to the spread of the inflammatory process to the walls of the ducts and gallbladder. The obliterated ducts may completely disappear, leaving no bands of fibrous tissue to indicate their position. The obliteration becomes complete at variable stages of intra-uterine life, and occasionally

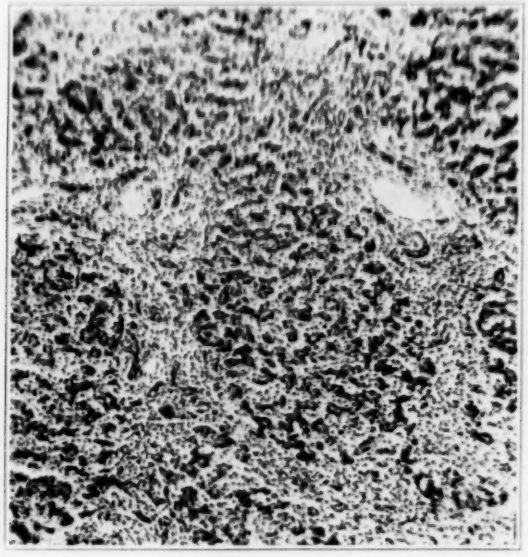

Fig. 4.—Liver section, showing necrosis of the liver cells, newly formed connective tissue encircling the acini, with marked infiltration of the lymphocytes and endothelial cells, and newly formed bile canaliculi.

not until after birth. The latter observation explains the late onset of symptoms in some of the cases. Cirrhosis of the liver is secondary.

Rolleston's view is that the cirrhosis of the liver, due to a toxin coming by way of the placenta, is primary,[20] and that this in turn causes a descending obliterative cholangeitis. The presence of cirrhosis in all reported cases, the mixed type of cirrhosis and the familial tendency as in hypertrophic biliary cirrhosis favor this view.

The conception that atresia is the result of fetal peritonitis with the formation of adhesions and constrictions has some adherents. From

20. Rolleston: Brit. M. J. 1:758, 1901.

necropsy reports showing the presence of adhesions and thrombi in the blood vessels, Schuster [21] concluded that the cause is a chronic ascending infection. Thrombi of the hepatic artery were present in our case but were recent and probably postoperative.

In most of his cases, Benecke [22] found that the atresia occurred at the lower level of the common duct in the region of the papilla of Vater. From this fact he elaborated the theory known as "Abschnurung Prozess." According to this idea, there is a tying, twisting or blocking of a normal duct by traction of the mesentery, rapid growth of the liver or proliferation of the epithelium lining the ducts, the lumina of which vary normally in size. Finally, obliteration of the ducts develops.

ETIOLOGY

Opinion is divided at present as to the etiology of this condition, and apparently no single explanation fits all cases. Trauma and similar factors during labor cannot explain the vast pathologic changes found immediately or soon after birth. There is no direct evidence that syphilis plays an important rôle. Vighold [10] stated that syphilis never causes it, and Hespe [23] expressed the belief that syphilis seldom causes atresia. Ashby [24] and Neumann [25] described single cases in which there was a definite history of parental syphilis. Chiari [26] reported a gummatous infiltration of the bile ducts with narrowing and constriction. The occurrence of cases in one of twins, reported by Feldman and Lawson,[27] tends to exclude syphilis as a cause. In four instances of Thomson's series of fifty cases, the parents had syphilis, but he did not assert that syphilis was a factor in the production of the anomaly even in these four instances. Familial occurrence is illustrated in two of Thomson's cases in which more than one member in the family were similarly affected. In one family, four infants had died with the same symptoms. Familial tendency is also strikingly illustrated in other hepatic pathologic changes, particularly the hypertrophic biliary cirrhosis of Hanot.

SYMPTOMATOLOGY

In reviewing the clinical signs associated with such pathologic changes as described, we find that they are those of a complete biliary obstruction.

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21. Schuster, H.: Frankfurt. Ztschr. f. Path. **33**:513, 1926.
22. Benecke, quoted by Rolleston: Brit. M. J. **1**:758, 1901.
23. Hespe, H.: Arch. f. Kinderh. **81**:137, 1927.
24. Ashby: Arch. Pediat. **1**:537, 1884.
25. Neumann: Berl. klin. Wchnschr. **30**:495, 1893.
26. Chiari: Prag. med. Wchnschr., 1885, vol. 10, no. 47.
27. Feldman, W. M., and Lawson, M. A.: Lancet **2**:113, 1924.

Jaundice is present at birth, as in our case, or very soon after, in the majority of babies. Feldman and Lawson [27] reported a case in which jaundice did not appear for three weeks. In Thomson's cases, jaundice appeared at birth in nine cases, on the second day in nine, third day in three, on the seventh day in four, after two weeks in six and in about three weeks in three. In Kostlin's [28] case, jaundice did not appear for six months. In some instances the delayed onset of jaundice may be explained by the fact that the liver is able to store some of the bile pigment until the concentration of the latter is too large, when it is absorbed into the circulation. Some other explanation will have to be offered for the late onset of jaundice in Kostlin's case, unless it is assumed that the obliteration was not completed until later. However, whether the jaundice is absent or slight at or soon after birth, it becomes progressively worse. In some cases the skin assumes an olive green color.

In our case the stools were dark green (meconium) for the first week. This seems to have been a fairly common observation by other authors. In Thomson's cases, ten of fifty patients passed dark green meconium for the first week even though some were jaundiced at birth, as was our patient. Many explanations are offered for this. Some investigators state that the green color is due to bacterial changes in the intestines, and others that it may be a chemical compound formed by mercury, which is often administered to these infants with sulphur. It is not reported whether or not chemical examination for bile has been made during the meconium stage. Meconium is normally dark green, due to bile pigment, and begins to be formed at about the fourth month of intra-uterine life. It is, therefore, possible to explain the occurrence of normal meconium in such instances if one assumes that the atresia takes place in later intra-uterine life. In all cases the meconium is followed by a colorless putty-like or greasy stool containing no bile pigment. In the course of time, a slightly yellow stool may be observed, but this is probably due to slight bile leakage into the intestines from the circulation.

The urine is usually highly colored, stains the diapers and on chemical examination contains bile pigments. The liver is usually large and may extend to the umbilicus. The spleen may or may not be enlarged.

Hemorrhages into the skin and mucous membranes are often described. Such hemorrhages were noted in fully half of Thomson's cases. These hemorrhages may occur in any part of the body, and usually constitute a bad prognostic sign. Such a symptom is common in long-standing cases of jaundice from other causes and may be due to a substance not detoxified by a diseased liver. This substance acts as a hemolysin. There were no hemorrhages in our case.

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28. Kostlin, quoted by Holmes, J. B.: Am. J. Dis. Child. **11**:405 (June) 1916.

The pulse is not slowed, as might be expected, nor is itching marked because of the absence of appreciable bile acids in the blood.

Nutrition and metabolism are affected in many ways. The nutrition is good in the early stages of this condition. Vomiting is not a common symptom. The fallacy that emaciation accompanies this disease led some physicians to doubt our diagnosis, since the infant was well nourished and retained its food well (see fig. 2). It is true that emaciation does occur, but not until later in the course of the condition; it should certainly not be expected at an early age. Bile is an aid to the digestion of fat, but even in its absolute absence some of the fat is absorbed and the digestion of other foods is hardly affected. In metabolic studies, Fleming,[29] Walker,[30] Niemann [31] and others have shown that in such cases only about 40 per cent instead of the normal 90 per cent of fat is absorbed, leaving large quantities of unabsorbed fat in the intestines. The absorption of nitrogen is about 86 per cent within the normal range. The absorption of phosphorus is good. The absorption of calcium is poor, because it is related to the intake of fat. Fat-splitting is usually good. Alfred Hess [6] made interesting observations by the use of the duodenal catheter in determining the excretion of pancreatic ferments. He noted that occlusion of the pancreatic ducts frequently accompanies atresia of the biliary ducts. In such cases, because of the absence of pancreatic ferments in the intestines, digestion as a whole is much impaired.

The van den Bergh test usually gives the direct reaction. An indirect reaction may also be obtained, as in our case (biphasic). A case with an indirect reaction alone has been described by Feldman and Lawson.[27]

PROGNOSIS

Cases of complete biliary atresia are invariably fatal. The average length of life is about ten weeks. In Thomson's cases, eleven patients lived less than one week; eight more than one week, but less than a month; fourteen from one to four months; sixteen from four to six months, and two, eight months. Lavenson [8] found that in sixty-two cases only three patients lived longer than eight months (two patients, nine months; one, eleven months). Porter's [32] patient lived fourteen months. Cases of longer duration have been described. Treves' patient was successfully operated on, at the age of 18 years, after jaundice of

29. Fleming, G. B.: The Respiratory Exchange in a Case of Biliary Atresia, Am. J. Dis. Child. **23**:66 (Jan.) 1922.

30. Walker, I. J.: Boston M. & S. J. **196**:734, 1927.

31. Niemann: Ztschr. f. Kinderh. **4**:152, 1912.

32. Porter, in Abt, I. A.: Pediatrics, Philadelphia, W. B. Saunders Company, 1924, vol. 3, p. 645.

sixteen years' duration.[33] It is questionable whether the latter cases fall into the group of congenital atresias.

TREATMENT

In Ladd's [34] series of twenty cases, eleven patients were operated on. Eight of the eleven were amenable to surgical drainage of the bile, and of these six have recovered. In Holmes' series of cases, about 16 per cent had atresia of the common duct, but either the hepatic or the cystic duct was patent. These are amenable to surgical treatment. In our case the atresia was so complete that no surgical help was possible.

SUMMARY

Congenital atresia of the bile ducts is one form of hepatic anomaly frequently encountered in earliest infancy.

The symptoms are those of complete obstruction of the bile passages.

The prognosis is bad in cases of complete atresia.

When a diagnosis of complete biliary obstruction has been established, exploratory operation should be performed with the hope that the anomaly of the bile passages might be of such a nature that a communication with the intestines might be effected.

A case of complete biliary atresia not amenable to surgical correction is here described.

33. Treves: Practitioner **62**:18, 1899.

34. Ladd, W. E.: Congenital Atresia and Stenosis of the Bile Ducts, J. A. M. A. **91**:1082 (Oct. 13) 1928.

INFECTIOUS MONONUCLEOSIS *

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Recently, there came under my observation an infant aged 7 months, who had an acute glandular swelling, associated with fever, an enlarged spleen and secondary anemia. The secondary anemia and the blood picture made the diagnosis of an acute lymphatic leukemia very suggestive. Repeated blood studies and the subsequent course of the disease, however, showed that the condition was a sporadic case of infectious mononucleosis. The rarity of this disease in its sporadic form in infants warrants the reporting of this case.

REPORT OF CASE

History.—A boy, aged 7 months, was admitted to the hospital with a complaint of fever and swollen glands. The family history was nonessential. There was no history of any chronic or recent acute illness in the family.

The child was born at full term after a normal delivery. At the age of 1 month, he had a mild case of impetigo, which cleared up rapidly under local treatment.

At the age of 3 months he had a slight gastro-intestinal disturbance which cleared up in two days. During the month before I was consulted, the infant had not seemed to be well. He was irritable and fretful, at times refusing food, but showing no fever. There were no other symptoms of any illness. The child had received a modified, weak solution of a proprietary infant food with about 12 calories to the pound of body weight; he had not received orange juice or cod liver oil. Three days before I saw the child, he began to have a temperature varying from 101 to 102 F. The family physician thought that the fever designated some gastric disturbance and treated the infant accordingly. A blood smear was examined for malarial parasites, but none was found. The morning the baby was sent to me for examination, especially with regard to the blood, he was found to have a generalized glandular enlargement.

Examination.—On admission to the hospital, physical examination revealed a poorly nourished boy of 7 months of age, who weighed 12 pounds and 8 ounces (5670 Gm.) and had a temperature of 101.4 F. The baby lay quietly on the examining table; he appeared drowsy, but was irritable when molested, and did not seem acutely ill. The muscles were flabby and the subcutaneous tissue of poor tone. The skeletal system showed a slight enlargement of the epiphyses of the long bones at the wrists and ankles. Otherwise it was normal. There was a generalized glandular enlargement involving the anterior and posterior cervicals, the axillary, epitrochlear, inguinal and popliteal glands. The glands were discrete and elastic but apparently not tender on palpation; they were about the size of lima beans.

The skin and mucous membranes were clear but pale. There were no hemorrhages, petechiae, exanthems or enanthems.

* Submitted for publication, Feb. 25, 1930.

The head was enlarged, with prominent anterior and posterior bossing. The circumference was 17.5 inches (49.53 cm.) and the anterior fontanel admitted three finger tips. The eyes, ears and nose were negative for symptoms. There were no teeth, and the tongue and gums were clear. A slight injection of the pharynx was noted, and the tonsils were normal.

The neck was normal, save for enlarged glands. The chest was normal in size and shape, measuring 15 inches (42.55 cm.) in circumference and exhibited no rosary. The lungs were clear throughout; the heart was normal. The abdomen was soft, with a fair muscular tone. There was no spasticity. The spleen, easily palpable and elastic to palpation, reached to the umbilicus in the anterior axillary line. The liver was palpable just at the margin of the ribs. No other masses were felt.

The genitalia were those of a normal male infant. The extremities were normal. The blood picture showed: hemoglobin, 55 per cent; white blood cells, 44,200. The differential count was: polymorphonuclears, 16 per cent; eosinophils, 0; basophils, 0; small lymphocytes, 5; large lymphocytes, 2, and atypical lymphocytes, 77. The total mononuclear count was 84 per cent. The red cells were

Blood Studies in Case of Infectious Mononucleosis

Date	Hemoglobin	White Blood Cells	Polymorphonuclears	Eosinophils	Basophils	Lymphocytes			
						Small	Large	Atypical	Total
7/ 1/29	55	44,200	16	0	0	5	2	77	84
7/ 5/29	48	20,400	13	2	0	10	8	67	85
7/ 9/29	46	15,000	35	0	0	10	5	50	65
7/12/29	48	14,500	41	0	0	9	10	40	59
7/19/29	44	14,900	27	0	0	62	0	11	73
8/ 2/29	53	15,800	37	3	0	49	4	7	60
9/ 4/29	55	9,400	30	1	0	60	8	1	69
10/23/29	50	9,700	27	0	1	63	9	0	76
2/ 7/30	55	8,700	43	2	0	40	15	0	69

typical of a secondary anemia. The differential counts were all checked with the Goodpasture peroxidase stain.

The atypical lymphocytes appeared as follows: The cells were slightly larger than normal polymorphonuclears and were comparatively uniform in size. The nucleus was not oval, but had an indentation, slight or marked, giving it a kidney-shape. The nucleus might fill the entire cell, or there might be a definite ring of protoplasm around it; it did not stain a uniform color throughout. No nucleoli were seen, and the protoplasm looked like ground glass, with no granules. The entire cell stained dark with Wright's stain. These cells could be readily confused with the abnormal lymphocytes appearing in an early lymphocytic leukemia.

Although the child had manifest severe rickets, and the blood picture showed lymphocytosis, a tentative diagnosis of acute lymphatic leukemia was made because of the marked anemia.

The child was brought back to my office four days later. His daily temperature had been 101 F. The physical examination revealed no changes in the general condition. The blood picture at this time showed: hemoglobin, 48 per cent; white blood cells, 20,400. The differential count was: polymorphonuclears, 13 per cent; eosinophils, 2; basophils, 0; small lymphocytes, 10; large lymphocytes, 8, and atypical lymphocytes, 67. The total lymphocyte count was 85 per cent.

At this time, the child was started on a treatment which consisted of 12 drops of viosterol and exposures to the alpine light daily. Further blood studies were

made at intervals, as shown in the accompanying table. The temperature returned to normal eight days after the onset of the disease. A gradual decrease was noticed in the size of the spleen and glands. They had returned to normal size three and a half months after the child was first examined. Under a routine diet of concentrated modified milk formula and the continued use of viosterol, the appetite and general condition showed definite improvement. There was no return of the fever or glandular swelling. The last examination was made seven months after the onset of the disease.

COMMENT

In 1889, Pfeiffer [1] described a new clinical entity which he called Drüsenfieber, or glandular fever. The condition as he found it was an acute infectious process met with in children between the ages of 5 and 8; the characteristic observation, in addition to fever, was enlarged and tender lymph glands; the onset was usually sudden, with fever, restlessness and pain in the extremities; the fever lasted from one to five days. Soon after the onset, the cervical glands became swollen and painful. On the third or fourth day, the liver and spleen were found slightly enlarged. With the subsidence of the fever, the children felt well and appeared normal save for the glands, which remained enlarged but no longer tender, and which returned to normal size gradually. No examinations of the blood were made in Pfeiffer's cases.

In 1896, West [2] described an epidemic of glandular fever in Ohio, finding ninety-six cases in forty families, and the following year a full discussion of this condition by Williams,[3] who cited several new cases, appeared in the *Lancet*. Neither of these two men, however, mentioned the blood picture.

It is to Turk [4] that the credit is due for being the first to call attention to the changes in the blood. In 1907, he reported three cases of acute infection characterized by a marked increase in the mononuclear cells of the blood. Despite his suggestion, many authors continued to report cases of glandular fever without studying the blood, and Haas,[5] in reporting twelve cases in 1912, went so far as to say that he found nothing unusual in the blood. However, subsequent work by Cabot,[6] Marchand,[7] Sprunt and Evans,[8] Longcope,[9] Bloomfield [10] and others has

1. Pfeiffer: Jahrb. f. Kinderh. **29**:257, 1889.
2. West: Arch. Pediat. **9**:889 (Dec.) 1896.
3. Williams: Lancet **1**:162 (Jan. 16) 1897.
4. Turk: Wien. klin. Wchnschr. **22**:15, 1907.
5. Haas, Sidney V.: Acute Glandular Fever in Children, Am. J. Dis. Child. **3**:241 (April) 1912.
6. Cabot: Am. J. M. Sc. **145**:335, 1913.
7. Marchand: Deutsches Arch. f. klin. Med. **110**:359, 1913.
8. Sprunt, T. P., and Evans, F. A.: Bull. Johns Hopkins Hosp. **31**:410, 1920.
9. Longcope, W. T.: Am. J. M. Sc. **164**:781, 1922.
10. Bloomfield: Progrès méd. **121**:171, 1924.

verified the earlier work of Turk and demonstrated that the glandular fever of Pfeiffer is a distinct clinical entity associated with a relative increase in the mononuclear cells of the blood. It is now generally conceded that glandular fever and infectious mononucleosis are one and the same condition, and the term infectious mononucleosis is being adopted as the preferable name.

The cause of this condition is unknown. In an intensive study of 105 cases, Rohner, Baldrige, and Herman [11] were unable to arrive at any definite conclusions as to the etiology, in spite of throat cultures, blood cultures and examination of excised glands. Most writers agree with Longcope that infectious mononucleosis is a definite entity of specific, but unknown, etiology. Various forms of streptococci, staphylococci, Vincent's organisms and diphtheroid bacilli have been pronounced the infectious agent, but careful study has failed to prove this.

The disease is infectious and appears in epidemic and sporadic form, and several epidemics have been reported. Carlson, Brooks and Marshall [12] have recently reported an epidemic in Wisconsin of 838 cases, 79 of which they were able to study carefully. Davis [13] also reported a recent epidemic of 9 cases from a nursery in Chicago in which all of the infants were less than 2 years of age. Sporadic cases are only seen occasionally, but it is possible that many of these go undiagnosed, the condition being thought of as a simple cervical adenitis. On the other hand, many cases are reported as glandular fever but the reports are not complete, since the essential blood symptoms are not recorded. Thus in 1924, Bloomfield could find less than 40 cases adequately studied, but since that time many authentic cases have been added to the literature.

Children of school age seem to be most susceptible, although infants and adults may also be affected, especially in epidemics. Males seem to be slightly more susceptible than females.

Since the disease is so rarely fatal, pathologic studies have been most meager. Outside of a lymphatic hyperplasia of the involved glands, no distinct pathologic lesions have been found in the body.

The blood picture is the most interesting, and at the same time the definite pathognomonic factor in the disease. As stated, there is a relative increase in the monuclear elements of the white blood cells. Turk, Çabot

11. Rohner, F. J.; Baldrige, C. W., and Herman: Proc. Soc. Exper. Biol. & Med. **23**:221, 1925.

12. Carlson, G. W.; Brooks, E. H., and Marshall, V. F.: Wisconsin M. J. **25**:176 (April) 1926.

13. Davis, Clara M.: Acute Glandular Fever of Pfeiffer, J. A. M. A. **92**:1417 (April 27) 1929.

and others in their early studies identified these as belonging to the lymphocytic family. In 1919, Saunders [14] advanced the theory that they were not lymphocytes but were nongranular myeloblasts. Subsequent work with the peroxidase stain has shown that the early contention was the right one, and that these cells are lymphocytic in origin. The total number of leukocytes is almost always elevated, varying from 20,000 to 40,000, although, as stressed by Bloomfield [10] and Major,[15] there may occasionally be a leukopenia. There is often a concomitant decrease in the actual number of polymorphonuclear cells of the blood; Longcope found only 2,000 of these per cubic millimeter in one case. Bloomfield described the blood picture as follows: In addition to the normal small lymphocytes and large mononuclears, the blood shows another type of cell which has been well spoken of as the pathologic lymphocyte. It is this third type of cell which predominates and to which particular interest is attached. These cells are somewhat larger than the small lymphocyte and contain kidney-shaped, slightly lobulated or Rieder-type nucleus, staining deeply with Wright's or Hasting's stain. They are usually without nucleoli and are often eccentrically placed in the cell. Sometimes the nucleus almost fills the cell, but at other times it is surrounded by a fair amount of basophilic protoplasm of ground glass appearance, which does not contain any definite granules. The abnormal cells do not show any granules when stained with the peroxidase stain.

These lymphocytes, normal and pathologic, are usually found to comprise from 40 to 80 per cent of the total number of leukocytes, with a higher percentage in sporadic cases. Chevallier [16] reported one case with a total white cell count of 22,000, of which 93 per cent were lymphocytes and mononuclears.

The clinical picture is rather characteristic. The incubation period is ordinarily from 5 to 10 days. The onset is usually sudden, with a rise in temperature (102 to 103 F.). There is frequently a slight nasopharyngitis with sore throat and a general feeling of malaise. In some of the cases there is acute abdominal pain, general myositis, vertigo and faintness, and in one case reported, there was epistaxis.[17] In two or three days, the lymph glands become enlarged and sometimes painful; they are hard and elastic. On physical examination, the patient appears to be uncomfortable and feverish, but not acutely ill. There is frequently a macular, rose-colored rash on the chest, abdomen and extremities. There is usually a slight injection of the pharynx. The most characteristic feature, however, is the enlargement of the lymph glands. The most

14. Saunders: J. Lab. & Clin. Med. **4**:344, 1919.
15. Major, R. H.: J. Kansas M. Soc. **24**:42, 1924.
16. Chevallier, P.: Bull. et mém. Soc. méd. d. hôp. de Paris **51**:573, 1927.
17. Burnet, J.: Edinburgh M. J. **34**:89 (Feb.) 1927.

frequently involved group is the superficial posterior cervical group, as well as the group which is usually affected first. Other groups may be involved, including the anterior and deep cervical, the axillary, epitrochlear and inguinal. There is also enlargement of the liver and spleen. The acute abdominal pain is probably due either to an enlargement of the mesenteric glands or to a hepatitis.

The acute symptoms subside rapidly. The high temperature lasts from 2 to 24 days, following a regular or irregular course. The fever usually subsides gradually, although in a small epidemic of 10 cases, the temperature fell by crisis in 9 on the fourth or fifth day.[18] The glands return to normal size slowly; at times months are required for this change. The blood picture returns to normal in a somewhat shorter time, although frequently it is several weeks before a normal differential count will be encountered.

Fortunately, complications are rare. Suppuration of the glands has been reported, but this is probably due to a secondary infection. Carlson, Brooks and Marshall found this complication in 8 of 79 cases, and in each case they found *Staphylococcus aureus* in the suppurating gland. Hemorrhagic nephritis is occasionally met with, and it is probably the most serious complication. Most writers claim that relapses do not occur, although Davis reported five relapses in nine cases in an epidemic in infants. Mild anemia may be found in the late stages, especially in infants. Mason[19] reported one case in which there was jaundice, and Craik[20] one with bleeding from the gums. I have been unable to find any report of a case in which death could be attributed to infectious mononucleosis.

The diagnosis is not always easy to make. Jager[21] speaks of cases accompanied by severe abdominal pain which simulate an acute abdominal condition. The four conditions, however, which are most likely to be confused with the condition are tuberculosis, typhoid, Hodgkin's disease and acute leukemia. A careful physical examination with accurate blood studies will usually rule out the first three. When there is acute leukemia, the difficulty in making a diagnosis is often great, and to attempt to give a prognosis is most embarrassing. Careful studies of the blood smear with the peroxidase stain will rule out myelogenous leukemia. But acute lymphatic leukemia and infectious mononucleosis may appear almost identical in the early stages, as I tried to bring out in the case reported. It is only by careful and repeated studies of the blood that a definite conclusion can be reached. The main

18. Leman: New Orleans M. & S. J. **81**:187 (Sept.) 1928.
19. Mason, V. R.: California & West. Med. **29**:187, 1928.
20. Craik, R.: Brit. M. J. **1**:1056, 1927.
21. Jager: J. Missouri M. A. **24**:15 (Jan.) 1927.

point in the differential diagnosis, as stressed by Lucas,[22] is that in infectious mononucleosis there are: (1) absence of anemia, (2) absence of any tendency to spontaneous hemorrhage, (3) a much less striking increase in the lymphocytic elements of the blood and (4) a relatively brief and self-limited course. Yet even with these points in mind, the diagnosis frequently is extremely difficult to make in the early stages.

As stated, the prognosis is excellent. Bass and Herman[23] have followed cases over a period of six years and have found no relation to leukemia. They conclude that infectious mononucleosis leaves no lasting effect on the patient.

SUMMARY

A case of infectious mononucleosis in a baby, aged 7 months, is reported with a general discussion of the disease. Especial reference is made to the difficulty in diagnosis between infectious mononucleosis and acute lymphatic leukemia in the early stage.

22. Lucas, W. P., and Washburn, A. H.: Blood and Blood-Building Organs, New York, D. Appleton & Company, 1928, vol. II.

23. Bass, M. H., and Herman, H.: M. Clin. North America 9:589, 1925.

GONORRHEAL RHINITIS*

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This case is reported because a search through the available literature failed to reveal any mention of similar cases other than the single instance reported by Weiner Framm.[1] In his case, the condition developed a few days after the delivery of the child from a mother suffering from gonorrheal urethritis and endocervicitis and manifested itself by development of a purulent nasal discharge accompanied by bleeding. A smear taken from the discharge showed large numbers of intracellular and extracellular gram-negative diplococci, and cultures had the characteristics of gonococci. In this case the child developed complications of ophthalmia and arthritis, probably both due to metastatic infection.

In view of the extreme scarcity of literature on the subject, the following case is reported.

REPORT OF CASE

M. M., a girl, was admitted to the hospital on Dec. 10, 1928, at the age of 1 year. She was well nourished and well developed, had no complaints, and was one of twins who accompanied the mother to the hospital. The mother was pregnant and suffering from gonorrheal endocervicitis. On admission it was noted that the child had a vaginal discharge, which on smear showed many gram-negative extracellular and intracellular diplococci with the characteristics of the gonococcus. The twin, a boy, was not affected. A diagnosis of gonorrheal vulvovaginitis was made, and the patient was isolated. Treatments consisting of vaginal instillations of surgical solution of chlorinated soda in olive oil were given daily, and the vaginal smears were negative on March 18, 1929. There was a relapse, however, from August 16 to October 2, with positive smears, and again on November 12 there was an exacerbation with renewal of discharge and positive smears for the gonococcus. In conjunction with this exacerbation, the child developed a profuse purulent and bloody discharge from her left nostril. This discharge was very profuse, making it difficult to examine the nose. The nasal mucous membranes were greatly swollen and red, but no foreign body could be located. There was some excoriation of the upper lip, and the discharge kept dripping from the posterior nasopharynx into the throat.

The patient's general health was not affected. The temperature ranged between 99 and 100 F. Respirations were 25; the pulse rate was 110. The leukocytes numbered 9,750, and the differential blood count showed: polymorphonuclears, 44 per cent; lymphocytes, 50 per cent; endothelial cells, 4 per cent, and eosinophils, 2 per cent. On the appearance of the unilateral nasal discharge and before the smears were examined, the child was given 10,000 units of diphtheria antitoxin intramuscularly. Examination of the smears, however, showed many intra-

* Submitted for publication, March 4, 1930.

1. Framm, Weiner: Deutsche med. Wchnschr. **51**:472 (March 20) 1925.

cellular and extracellular gram-negative diplococci which on culture had the characteristic growth of the gonococcus. No evidence of diphtheria was found.

Treatment with ice-cold irrigations of boric solution, a spray of epinephrine and nose drops of 10 per cent mild silver protein were begun immediately, but the response was slow. On December 2, the smears were negative, and on December 15, the discharge had completely disappeared. During the period of treatment, the child's arms had to be restrained to keep her from conveying the infection to the eyes.

COMMENT

This case is similar to that of Framm in that the characteristics of the discharge were identical, being profuse, purulent and bloody. The treatment used in this case was patterned after that used by him, with the exception of the ice-cold irrigations. The difference in age of the patients serves to stress the probable avenues of infection. In Framm's case it was probably in the process of delivery that infection developed, while in the case reported the fingers were probably responsible for carrying the coccus to the nose from the vagina. The exacerbation of vaginitis in conjunction with the condition would suggest this mode of infection. Fortunately, the patient developed no complications, although Framm's patient had both arthritis and ophthalmia.

The diagnosis of gonorrheal rhinitis is difficult because of the morphologic likeness between the gonococcus and the meningococcus. They stain alike with Gram's stain and are both found intracellularly and in pairs. In addition, the nose is the normal habitat of the meningococcus, while the gonococcus is probably foreign to this location. Therefore, in order to differentiate the organisms, it is necessary to observe their growth on culture mediums. The cultivation of the gonococcus from the nasal secretions is difficult, as it produces small colonies, and, as the organism is delicate, it requires a medium of narrow p_H range. The inoculation of the secretion on mediums by means of a platinum loop is impracticable as it is quickly overgrown by the contaminating organisms. I was able to obtain satisfactory cultures only by first dissolving the loopful of secretion in physiologic solution of sodium chloride and then plating. Wertheim's medium was used, and a typical growth was obtained at the end of twenty-four hours, after which it became overgrown with contaminants and died out. It was found impossible to grow the gonococcus by transplanting it to another plate, and for this reason I could not get a pure enough culture to obtain sugar reactions. An attempt to grow it in spinal fluid met with failure.

It is interesting to note that in spite of the scarcity of reported cases, this disease has not gone unobserved. In the "System of Medicine" edited by Tice,[2] there is a paragraph dealing with nasopharyngitis

2. Tice, Frederick: System of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1928, vol. 3, p. 453.

of gonorrheal origin, and in Coakley's [3] "Diseases of the Nose and Throat" mention is made of a persistent rhinitis occurring in newly born infants of gonorrheal parents.

It would seem, therefore, that gonorrheal rhinitis is more common than its very scanty mention in the literature would indicate. It should be considered in the differential diagnosis of every case of bloody nasal discharge along with diphtheria, syphilis and foreign body. Although the disease is mild in itself, complications such as arthritis, sinusitis, otitis media and ophthalmia may be extremely severe, and may cause permanent debility. Therefore, it is a disease to be recognized for what it is so that proper treatment may be instituted to guard against these complications.

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3. Coakley: Diseases of the Nose and Throat, ed. 4, Philadelphia, Lea & Febiger, 1908, p. 83.

Progress in Pediatrics

THE PSYCHIATRIC ASPECTS OF ENURESIS*

FORREST N. ANDERSON, M.D.
LOS ANGELES

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* From the Graduate School of Medicine, University of Pennsylvania, and the Philadelphia Child Guidance Clinic.

* The material for this study was gathered over a period of approximately eleven months, during which one-half of my total time was devoted to obtaining the data on which the study is based.

* The material incorporated in this presentation represents work of the third and final year in the course in neuropsychiatry of the Graduate School of Medicine, University of Pennsylvania. The work was carried on under the general direction of the three following men: T. H. Weisenburg, M.D., Vice-Dean of the Department of Neuropsychiatry; F. H. Allen, M.D., Director, Philadelphia Child Guidance Clinic; George Stevenson, M.D., Director of Community Clinics, National Committee for Mental Hygiene.

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Bibliography

It has long been recognized that enuresis presents one of the most frequent problems in the management of children, at home, in the clinic and in the institution. Since orthodox medical methods have never proved highly efficacious, it has been increasingly felt by many workers that psychic and emotional factors play a large part in the problem. The undertaking of a lengthy and detailed study of this subject, based on case material, was assigned to me, and these observations and results are here set forth. Obviously, certain limitations were necessary, so that it was early decided to eliminate treatment by strictly medical measures.

The material available came from several sources:

Philadelphia Child Guidance Clinic:	
Cases studied personally	55
Cases studied through detailed case records	55
Cleveland Child Guidance Clinic Los Angeles Child Guidance Clinic	26
Cases studied through detailed case records of:	
Children's Hospital of Philadelphia Outpatient Clinic	13
Orthopaedic Hospital and Infirmary for Nervous Disease, Outpatient Clinic (Philadelphia)	6
Pennsylvania Hospital for Mental and Nervous Disease	2
Pennsylvania Hospital for Mental and Nervous Disease, Outpatient Clinic	2
Private cases of Philadelphia neuropsychiatrists	2
Personal—through friends	5
Institutions:	26
Friends Home for Children	5
Presbyterian Orphanage	7
Elliott House	9
House of the Holy Child	5

This number exceeds slightly the number of positives, since the personal cases were officially transferred to the Child Guidance Clinic in order to provide for more thorough study, e. g., psychologic tests, etc. Further, certain of these cases were studied in hospitals on transfer from the clinic. Exactly one half of this series was under my personal observation. There is also a small series of children without enuresis, but presenting clearcut neuropsychiatric diagnoses; these were studied at the Orthopaedic Hospital outpatient clinic.

Finally, there occurs a series of fifty normal control cases, based on children of high type and educated families, who have cooperated splendidly in making possible this phase of the investigation. These are discussed under the respective headings.

REVIEW OF THE LITERATURE

PHYSIOLOGY AND INCIDENCE

Physiology of Normal Micturition.—The authorities, while not pretending to explain the act of micturition, nevertheless agree fairly well on some such situation as follows: The pelvic nerve (second to fourth sacral) is motor to the detrusor muscle, producing contraction of this muscle and relaxation of the urethra. The hypogastric nerve (eleventh thoracic to second lumbar) is at least thoretically inhibitory,[5] and it has been shown in the cat that a complete antagonism of action exists

between these two nerves. Probably it is the normal tonic contraction of the urethra that maintains the urine in the bladder. Fundamental to this end, too, is the internal sphincter, unstriped muscle continuous with the middle circular coat of the musculature of the bladder. Amberg pointed out that this sphincter is a functional rather than an anatomic structure, however, and the question seems unsettled as yet.

Given some such state of affairs, it can be considered that distention of the bladder causes afferent impulses to reach the spinal centers, whence originate impulses for contraction, traveling via the pelvic nerve. There is probably a third, or voluntary, element in the innervation, viz., to the striated musculature of the urethra—the bulbocavernosus muscle —via the pudic nerve.

It has often been suggested that a functional weakness exists in the sphincteric muscle of children, placing it as subsidiary to the relatively stronger detrusor. Others consider the subject from the nerve basis, insisting on the presence of local spasm due to hypervagotonia of the pelvic plexus (Sicard [189]).

All of the aforementioned factors consider only the lower reflex paths, whereas it is known that some sort of cerebral control exists over the process. Just what happens is largely speculative, but in some way the spinal center comes under the influence of the upper motor neuron. This leads naturally to consideration of the localization of these functions in the higher portion of the nervous system. There has been much argument concerning these locations. The researches of Forster, Ader and von Kleist and his associates have pointed to the presence of a motor center in the region of the paracentral lobule, a center for the control of the emptying function of the bladder. Rietschel went further and predicated a "will center" somewhere in the frontal area, an indefinite inhibition center and probably subcenters in the region of the striate body. Moss quoted Sherrington as concurring in the localization of a vesical center in the region of the foot; others, such as Marburg and Czylharz, would place this in the general region of the hip areas. Perhaps, *a priori*, this would seem more logical.

All that concerns one in this discussion is the complicated nature of the neural paths effecting control; it is not purposed to discuss exhaustively the evidence for one or another path. But if one merely assumes a failure of the cortical control being gained over the lower or spinal centers, the phenomena of enuresis are, in a broad way, accounted for.

To one who is interested in the reflex pathways whereby local control over the bladder is obtained, the admirable discussion by Barrington [190] is recommended. He has shown that a center for the control of certain rhythmic movements of the bladder must originate cephalad to a plane transecting the posterior portion of the inferior colliculi and the midpons.

Prevalence.—To justify interest in the subject of enuresis one need only consider briefly some of the data on its incidence. Statistics are so extremely variable, according to general population, clinical institutions, etc., that it would be futile to attempt any summary of figures presented. Nevertheless, a few estimates are enlightening. Pese [86] found that in the children's asylum at Breslau, during the World War 30 per cent of all small children and 10 per cent of older children suffered with enuresis. Dunham [44] said that among 800 nervous children admitted to Phipps, between the ages of 5 and 16 years, 7 per cent were bed-wetters. Cimbal [188] concluded that it is a part of the problem of from 12 to 15 per cent of all nervous children.

Sex.—Closely connected with general prevalence is the question of sex prevalence. Among 226 cases cited by Schwarz [124], 148 patients were males. Among Grover's [54] 200 cases, 62 per cent were males. Burnet expressed the belief that it is probably more frequent in boys. Firth [14] had many more females than males in his series. Jacobs [94] stated that in one institution with which he was familiar containing 450 girls, only 8 were seriously affected; in another institution of 650 boys probably more than 100 had definite enuresis. Walker [127] said that the sexes are equally affected. In general, the opinion wavers between that of approximately equal incidence of the sexes and of a moderate preponderance among males.

Family History.—According to Cimbal,[188] from 30 to 40 per cent of patients with enuresis have enuresis in the family history. Occasionally this is mentioned elsewhere, particularly in texts.

CLASSIFICATION OF CASES

Almost every author of experience has more or less definitely classified his cases. Probably the broadest basis of division has been that on a physical versus a nonphysical or neurotic basis, these latter constituting the so-called idiopathic or essential type. More specifically the following may be cited:

Pototzky:
- Hyperexcitable or neuropathic
- Hypobulic or psychopathic
- Intellectually and emotionally moronic

Saxl and Kurzweil:
- Due to local irritation
- Due to general ailments
- Due to endocrines
- Due to urinary conditions
- Idiopathic

Walker:

Apathetic make-up, with atony of bladder
High strung, intelligent without deep sleep
Deep sleepers

Thursfield:

Congenital, those having it continuously from birth.
Acquired

Sundell:

Unconscious micturition, those with mental defect, petit mal or physical abnormality of bladder and urethra
Urgent micturition, those in whom the cause is first and foremost nervous

Collin:

Infantile
Digestive
Emotional

Moss:

Pathologic increase in the amount of urine
Reflex
Idiopathic, or functional
Endocrine

Hintze:

Bodily or mental retardation
Generalized physical observations, e. g., rickets or scrofula
Genital deformities
Acid urine

PHYSICAL BASIS

There is a shelf full of general and would-be specific discussion on the physical causation of enuresis. It is natural that it should be so. As physical medicine has always been in advance of mental medicine, it is to be expected that exhaustive physical examination and study should be made.

Ezickson [176] reported cases of intractable enuresis in which he found unsuspected cystitis and spina bifida, respectively, and he pleaded for more thorough physical study. Aguilar [60] was convinced that thorough study will usually reveal anomaly or disease, and only when such can be positively excluded is it permissible to label it "essential." Gottfried [80] reiterated that tenacious enuresis is often a result of subnormal development of the nerve tracts controlling bladder functioning. Bossert-Rollett [75] discovered that certain children when allowed to remain in bed all day had no enuresis, and concluded that a circulatory disturbance is basic in many instances. Krafft [88] expressed the belief that physical causes account for most cases.

An interesting study by Schroeder [193] of forty-four inhabitants (aged from 10 to 17) in a boarding school for dependent boys revealed the

following figures in this respect: overweight, 14 per cent; normal, 32 per cent; underweight, 54 per cent. Partridge [102] expressed the opinion that physical deviations can definitely be excluded in one half of her series among the feebleminded. On the other hand, the vast majority of the earlier articles in texts, in a general way, consider the physical condition as either basic or related. To summarize these articles would be but duplication of the standard texts of a decade past.

Cystitis.—A number of authors call attention to the frequency of cystitis in enuresis and would account for many cases in this way. Fleischner [15] averred that 20 per cent of the cases at his clinic are caused by colon bacillus infections of the urinary tract. Shore [24] presented case reports of cures based on treatment for cystitis with hexamethylene.

Digestive Disturbances.—Van der Bogert [25] expressed the belief that disturbances in the digestive function play an important rôle, and he presented as evidence the fact that the age occurrence of enuresis and digestive troubles is the same, and that the dietetic history of many enuretic patients shows gross errors. He concluded that "A fair percentage of cures by this method has made me exceedingly enthusiastic."

Diet.—Diet is lightly touched on as a general measure in many of the discussions; by only a few is a specific relationship believed to exist. Noeggerath [105] commented on the incidence of diets of potatoes and foods rich in salt among enuretic patients. Zappert [184] raised the significant questions as to why all enuretic patients are not influenced by diet and why all malnourished children with enuresis do not improve when the physical side is built up. He failed to find any anomaly in forty-nine cases; the other nineteen showed three types of anomalies: sacralization of the fifth lumbar, scoliosis and nonfusion of the posterior lumbar transverse process and the sacrum. Saenger examined every patient with enuresis with the roentgen rays, and only one had myelodysplasia. Among 81 cases of incontinence, West [19] found a percentage of 50.6 of spina bifida occulta, but among 100 men without enuresis he found practically as high a percentage, 48.

Myelodysplasia.—The relationship of defects in the structure of the lower spinal column, with assumed associated defects in the cord, has come in for discussion. The idea dates to Fuchs, but it has received confirmations and denials by many since that time. Proponents of the view include: Arnesen,[181] Cozzolino,[114] Morgagni,[120] Leopold [68] and Ezickson.[176] Leopold stated, "It is our firm conviction that not a few cases of enuresis in children are due to spina bifida occulta." Spiller presented two cases of persistent enuresis in boys, aged 18 and 14 years, on this probable basis. On the other hand, there is much weighty evidence against the theory. Hintze came to the conclusion that these spinal deformities are frequent observations in children and have

nothing to do with pathologic changes in the cord. Carrau [74] examined sixty-eight cases of enuresis with the roentgen ray.

TREATMENT; NEUROLOGIC ASPECTS

Atropine.—When one comes to a consideration of the drugs used for this condition, one is met by an almost limitless list. This is, of course, prima facie evidence of the nonspecificity of any drug, and one cannot but feel that something more than drug action has been responsible for cures in many of the cases.

At the head of the list stands belladonna, or its alkaloidal derivative, atropine. To enumerate the writers who have favored it would be to include probably one half of those included in the bibliography; indeed, it has been recommended by all save those who have lauded some particular drug or method of their own. Its mode of action has never been exactly clear. Nevertheless, it probably does exert some definite action in certain cases. No less an authority than Cushing (p. 336, ed. 6) said: "Perhaps this action in relaxing spasmodic contractions may also explain the beneficial effects obtained in cases of incontinence in children, in which belladonna has long been the most reliable remedy." Amberg (1923 [107] and 1924 [120]) found that in many cases contractions of the bladder occurred less frequently.

Thyroid.—Thyroid and pituitary extract probably rank next in favor. According to certain writers, e. g., Sundell [88] and Firth, a dulling of cerebral perception is the fundamental factor in the causation of enuresis. If this is true, thyroid should, *a priori*, have some effect, and it has been found actually to do so. Perhaps included in this group are mentally deficient or backward children, some of whom show generalized improvement under thyroid therapy, and in whom the decrease in enuresis may be merely a resultant of this more general alteration.

Pituitary Extract.—It is to be expected that with the great tendency to use endocrine therapy in all sorts of nonspecific cases, pituitary products should early come in for trial. The well known contractile effect of pituitary extract on smooth muscle, coupled with the belief of many that a relative hypotonia of the musculature of the bladder exists in enuretic persons, affords a possible rational basis for its employment. But one must remember that relaxation of detrusor tone is not in itself provocative of incontinence, rather would relaxation of the sphincter be, and how the substance could work on one muscle and not on the other is hard to state. Jacobs [94] reported excellent results in a group of institutional children. Of forty-nine cases, cure was effected in sixteen and great improvement in seventeen. Moss [103] used pituitary extract in thirty cases in doses of 3 grains (0.195 Gm.) daily. Fifty per cent were cured, and 25 per cent evidenced marked improvement.

He stated that he did not know its modus operandi. Blau likewise reported cure or improvement in 75 per cent of cases.

Testicular Extract.—Fischer [116] observed that many enuretic patients have unilateral or bilateral cryptorchidism, and concluded that testicular extract will be efficacious in such cases. He reported success in all but 21 of 500 cases. Oddly enough, he stressed the necessity of confidence and other intangible factors. Ergotoxine is favored by a few investigators because it is presumed to stimulate the motor myoneural junction, while ergamine, the other alkaloid of ergot, acts directly on unstriped muscle cells. The apparent paradox in this therapy disappears if one accepts the explanation that essential enuresis is due to an atony of the internal urethral sphincter, which relaxes without awaiting distention of the bladder.

Other drugs with no special rationale are: valerian, antypyrine (Gibbs [140]), rhus aromatica (Moss), tuberculin (Moss,[103] Langer [97]), salicylates (Krafft), takadiastase (Radcliffe [139]) and glycerin (Ochsenius [122]). Strychnine, arsenic and iron have been employed by a limited number of physicians, presumably on the general "tonic" theory invoked so often when specific remedies are not available.

Although limitation of fluids has been seen to be a cardinal principle in the treatment for enuresis by many, perhaps most, physicians, a definite minority actually favoring diuresis have used the less potent salts—acetates, citrates and benzoates. These and the phosphates have likewise been used to effect alteration in the acid-base reaction of the urine, under the impression that a too acid urine was frequently responsible for the trouble.

Camphor.—Pototzky [67] favored camphor in the treatment for the neuropathic type. Deangelis [77] reported improvement or cure in six of eleven cases after the use of 2 grains (0.13 Gm.) of camphor. This theory is based on the hypothetical sedative action of camphor on the genital zone. Pharmacologists have been wont to scoff at this, but in the "Handbuch" by Ewald and Heffler camphor is listed as of value in vesical tenesmus (also by Poulsson).

Epidural Injections.—An interesting method of treatment, provocative of much literature, is that of epidural injections of saline solutions. This procedure is favored by Aguilar,[60] who never hesitates to apply it when other medicines fail. Freeman [31] referred to this method as "far and away the quickest method of curing this pitiable complaint," an opinion based on several scores of cases.

The rationale of this test, introduced by Cathelin, is expressed as a pressure effect on the cord exerted through the fluid, resulting possibly in direct action on the filaments of the cauda and a reflex tonic effect on the lumbar centers. In essence, this method consists of injection, by

a needle about 6 cm. in length, of 10 cc. or more of physiologic solution through the membrane covering the sacral hiatus. In this manner the fluid gains the epidural space, extending from the end of the dural sacral to the first sacral vertebra. Cruchet and Carles reported remarkable results in several cases of pure nocturnal incontinence.

Empirically, this method has shown results, and is seen to have an apparent basis in physiology. But one can never divest oneself entirely of the idea that it may be acting as the source of a powerful suggestion. Nor is this suspicion allayed when one reads that the same brilliant results have been reported by the simple perineal injection of physiologic solution of sodium chloride (Serantes and Montes;[168] Salleras, quoted by the former authors).

Neurotic Basis.—Under the general terms "neurosis" and "neurotic" has been grouped a large number of persons suffering from enuresis. One might quote indefinitely from the literature. Thus, "As a result of my study I am tempted to say that the average case displays no tangible anomaly or infirmity definitely causative in nature" (Blau). Walker [197] said that children with enuresis are more liable to suffer later from functional disorders than are others. Dunham [44] stated: "Uncomplicated nocturnal enuresis is an element in the psychic regression of an unstable organism towards a more primitive biologic state." Herman expressed the belief that enuresis is a neurosis of the spinal center for micturition. Robson, after reviewing the general situation, came to the conclusion that, excluding gross disease, enuresis is primarily a functional nervous disorder. Klotz based his treatment on a "neuropsychopathic constitution."

Emotional Excitement.—It has frequently been noted that enuresis occurs frequently on nights following exciting days or evenings—extra vigorous play, arrival of relatives, tantrums and the like. This has led to the interdiction of such excitement by the attending physician; a majority of the standard works mention it in one way or another. Doubtless it has its basis in fact and is empirically sound advice, but one must always bear in mind that it is possibly "post hoc propter hoc" reasoning.

Depth of Sleep.—It is perhaps natural that attention was very early directed to the depth of sleep existing in enuretic patients. As mothers appearing at clinics so frequently complain of the unusual soundness of sleep of children afflicted with enuresis, it could not do otherwise than claim consideration. Many observers have commented on this factor; among those who favor it as a causal factor are: Pese,[66] Focher,[138] Weissenberg,[170] Bierens de Haan,[72] Pototzky,[67] Ochsenius,[122] Gottfried [80] and Berum.[172] De Haan perhaps expressed the point of view

typically when he stated that the sleep is so deep as to be below the threshold for the normal rousing reflex for the evacuation of the bladder, and that all that is necessary for a cure of enuresis is prevention of this deep sleep. Courtin approached this subject from an experimental point of view and came to the conclusion that the depth of sleep among enuretic patients is not different from that of other children, and that among bed-wetters just as many light as deep sleepers are to be found. Moreover, he felt that the maximum depth of sleep in no way coincided with the appearance of enuresis.

Dreams.—It is, perhaps, not to be wondered at that dreams should come in for study as possible illuminants on this condition. In part this may be accounted for by the psychoanalytic school and in part by the not uncommon observation that older children occasionally report vivid dreams of being seated on the toilet urinating and awakening to find the bed wet. But whether such a dream is the cause or the result remains uncertain. Schwarz [41] definitely favored the latter view. Weissenberg and Ochsenius (quoted by Lopez [80]) regarded them as of importance.

Hypnosis.—Closely allied to dreams is the subject of hypnosis, mainly, of course, from the therapeutic standpoint. Especially is this the case in certain of the earlier literature, when hypnosis had a wider vogue in general than is now the case. Narath [170] treated 182 patients between the ages of 5 and 28 years, with 76 per cent absolute cure and a definite improvement in an additional 17 per cent. Kleeman [144] considered hypnosis as fundamentally sound. Trommer,[11] at a meeting of the Hamburg Aerzbecher Verein, demonstrated several cases of persistent enuresis in which the patients were cured by hypnosis. Of a series of 133 cases, he reported cure in one-half and improvement in another one-third. Wetterstrand cited many excellent reports ranging down to children of 2½ years of age. Moreover, he considered the prognosis under this treatment most favorable when it occurred every night.

Routine Measures.—During the course of years of relatively unsatisfactory dealing with enuresis, a series of almost routine measures has developed, repeatedly reported in the literature and constituting the chief modes of treatment. Even the men who have enthusiastically championed "specifics" have hesitated to drop these measures. In the main, they are empiric, but founded on fairly sound theoretical bases. The individual measures of this group are differently stressed by various authors, but because of their widespread use it has seemed well to term them "routine measures."

Restriction of Liquids: This procedure has been so frequently advised as to be almost universal. Since it was observed that so many

children wet the bed early in the night, it was reasoned that if the bladder were not only drained at the time of retiring, but also provision taken to avoid the likelihood of its rapid refilling from recently ingested fluid, this critical period of early night could be safely passed. It is unnecessary to cite those favoring this plan; it includes almost every practitioner writing.

However, occasionally a voice is lifted against this practice. Thus, Thursfield [128] stated that no attempt should be made to restrict fluids, since such a course leads to the secretion of highly concentrated urine, likely to be exciting to the bladder. He even goes to the opposite extreme, by recommending diuresis with citrates. Krafft [85] likewise cautioned against the restriction of fluids.

Awakening at Certain Stated Intervals: These intervals vary widely, but in general favor is the plan of arousing the subjects early in the night, about 10 p. m. This is, of course, in recognition of the commonly observed fact that most enuresis occurs early in the night. Closely associated with this plan is the stressed demand that the child be thoroughly and completely awakened. Thom [131] has especially insisted on this. It has, certainly, very definite advantages, and would seem to be one of the most important plans in any treatment. It assumes the conscious basis of early habit training; it renders the possibility of sheer laziness being a factor very much less likely; it "conditions," or tends to condition, a lighter sleep at the time of accustomed awakening—all of which are fundamental in the formation of new substitutive or corrective habits.

Avoidance of Sleeping on Back: This has been a stock in hand method in the past. Based on the observation of greater activity of spinal centers in the supine position, as evidenced in dreaming, erections and enuresis, the idea has been worthwhile. But the modes of accomplishment of the desired end have not always been successful. Thus the plans of knotting a towel in the back, or of tying a spool at the back have been widely resorted to.

Elevation of Foot of Bed: This has often been advised on the theory that the pressure of the fluid on the sphincteric area predisposed to relaxation and consequent enuresis. No satisfactory proof for this has been adduced. It is favored, among others, by Saxl and Kurzweil [123] and by Carter.[76]

Hydrotherapy: Under the guise of cleanliness, shock, tonic effect, etc., the use of baths or local applications of water has been generally advised in the past.

Exercise of Sphincter: A considerable number of physicians have extended the widely accepted principle of exercise for increasing strength. They have reasoned that volitional endeavors to exercise the bladder sphincter would strengthen it, and have put forth the "stop-

start" plan. This consists simply in having the child consciously bring about a sensation of the flow of the urine for a few moments during micturition and then start it again, repeating this procedure several times daily. This is advised by Pisek [57] and Carter [58] among others.

Psychic Treatment.—Without going into any consideration of the real relation of psyche and physique, or as to whether mental treatment can effect alterations in an organic disturbance (and hence as to whether enuresis is thereby fundamentally shown to be nonorganic), one can cite many observers who definitely favor the psychic treatment for this disorder. Kleeman [144] favored reassurance, as well as hypnosis; Ochsenius [182] stressed the value of "willing" to awaken as a curative factor; Chandler [185] said that the child must be taught that the trouble is not so desperate, and that it keeps on because he keeps worrying. Wile and Orgel [183] admirably presented some interesting statistical evidence along these lines. Two series of fifty children each were treated with and without medication. The nonmedical regimen was the development of a desire to conquer the habit, coupled with assurance that it could be done. Results were 38 per cent cure in each series.

Even Focher,[138] who reported in glowing terms on endocrine therapy in a certain type, injected this interesting comment: "Das Kind muss stets das Gefuhl haben, dass man es gut mit ihm meint." (The child must always have the feeling that one means well.) Morichau-Beauchant [98] considered a fundamental of treatment for enuresis "explanation and gentleness." Pototzky,[102] an exponent of the camphor therapy, included suggestion in his armamentarium. Cameron, in an excellent article, stated that he regarded suggestion as the fundamental cause and treatment. Emerson [58] included suggestion as one of his chief reliances.

Training.—Those who consider training the essential thing are voicing their opinion more than formerly. One can do no better in expressing this point of view than to quote Blatz,[185] who stated that it can be shown that enuresis is a condition not due to mentality, size of family, grade in school, position in family nor chronological age, etc., but one that can be traced fairly definitely to faulty training. Further, he expressed the belief that it can be shown that the success of this treatment by development of suitable habits depends directly on the cooperation not only of the patient, but of the other members of the family. Thom [151] likewise favored this view. Thursfield [126] considered that nothing can replace the reeducation of the child who has enuresis. Karger [118] described how understandable it is that thirst may arise from breathing through the mouth, following rhinitis, and be continued as a habit. Wylder [188] and Emerson [58] likewise favored this view.

Conditioned Reflex.—The matter of training, of course, is essentially at one with the question of habit basis and reflex conditioning. Newlin [89]

considered the whole principle to be the simple procedure of anticipating the involuntary act of emptying the bladder by the voluntary emptying of the bladder, in other words, the establishment of proper habit. Karger [118] considered it on this basis largely and expressed the belief that the favorable effects of disagreeable drugs immediately following enuresis may be explainable as the development of a "regular pedagogic conditioned reflex in the child." Gibbs [140] concluded that it is a habit formation, and that even when the cause is removed the unconscious habit of emptying the bladder remains.

CAUSES

Psychoanalytic Views.—The psychoanalytic point of view of urethral eroticism is stressed by Stekel,[104] Klasi,[46] Sadger, Marcuse (quoted by Hamburger [45]), Abraham [89] and Herbert.[92] Stekel referred to the tendency of aged men to return to this habit, constituting a form of infantile sexual activity. Schwarz suggested the flight into enuresis as an escape from an intolerable situation. This, of course, implies that enuresis is a hysterical symptom.

The idea of Adler—of an inborn functional organ inferiority—finds favor with several authors—Schwarz, Eckstein and Noeggerath. More of these psychoanalytic points of view appear in the discussion of the present series.

Zappert, who presented the most exhaustive review of the recent literature, concluded his study with an idea rather at variance with any widely accepted point of view. "Where inclination to enuresis exists numerous factors can cause the phenomenon to appear, but what arises is the illness enuresis and not a symptom, i. e., enuresis exists as a disease per se." Zappert, too, admirably summed up the therapeutic endeavors against enuresis as being either symptomatic or suggestive. In the first group would fall restriction of fluid, awakening and use of urinals, and perhaps also rest in bed before sleep, restriction of the diet and general upbuilding of the body. All other measures are suggestion therapy, even the use of atropine, since he stated that it has not definitely been proved to have an actual action on the bladder.

ADDITIONAL FACTORS

Certain additional points remain to be considered because of their frequent occurrence in the literature as points of view.

Epilepsy.—The possible relation of enuresis to epilepsy has often been considered. Pestalozzi [88] spoke of an epileptic enuresis, as did von Pfister.[4] Zappert [109] remarked, however, that in his years of experience he had never found it necessary to weaken the rather clearcut

differential diagnosis between epilepsy and enuresis. Von During [156] likewise discussed this relationship.

Necessity for Circumcision.—Hamonic (quoted by Schwartz) reported good results with this treatment. In Grover's series, 51 per cent of the boys had been circumcised. This procedure is urged universally by writers of textbooks.

Tonsils.—It is not surprising that the tonsils and adenoids should come in for blame in this condition, as in countless others. Fischer (quoted by Schwartz [86]) found that 14 per cent of his patients with diseased adenoids had enuresis. Grover stated that in his 200 cases 36 per cent had the adenoids removed, without relief. Mygin (quoted by Ruhrah) found diseased adenoids in 75 per cent of 400 cases. Grubach (quoted by Ruhrah) found 14 per cent in 427 cases, and Llang (quoted by Ruhrah) found 16 per cent.

Heredity.—All sorts of opinion prevail on this topic, just as on every one in which heredity may possibly be a factor. Grover, in a study of 200 cases, found a family history of 56 per cent. Krafft [83] merely commented on the value of belladonna in the "hereditary form."

Relation to Intelligence.—Schroeder [193] reported as follows: Intelligence quotient below 70 in 7 per cent; intelligence quotient below from 70 to 80 in 25 per cent; below from 80 to 90 in 30 per cent; below from 90 to 110 in 36 per cent, and below from 110 to 120 in 2 per cent. Partridge [192] found enuresis present in about 10 per cent of the male population of the feebleminded inmates in the Vineland Training School.

Schroeder [193] reported the following periods of onset: infancy, 37 per cent; preschool period, 9 per cent; preadolescence, 2 per cent. The date of onset was undetermined in the other 50 per cent.

Reversal of Concentration of Urine.—Recently some interesting investigations have been carried on by Friedell [189] at the University of Minnesota, which indicate that in a small percentage of cases there is a failure of the normal capacity to concentrate urine during the night. This came out in the search for reasons as to why a certain percentage of persons failed to respond to psychotherapy administered by hypodermic sterile water. He found this persistent reversal in the cases in which failure occurred (13 per cent of thirty-nine cases).

Pressure.—Some interesting experiments were carried out by Weitz and Gotz [85] which for a time seemed to explain enuresis partly on psychophysiologic grounds. These investigations showed that by taking pressure tracings of the bladder, contractions frequently coincided with desire to micturate. This condition obtained in normal persons, but in enuretic patients such contractions often occurred without a simultaneous desire on the part of the patient. If this was the situation, one had to

deal with a materially heightened threshold of sensory stimuli in the case of enuresis. This theory attracted considerable attention, and the experiments were repeated by Amberg. He found [109] that such lack of sensation was the exception rather than the rule, and that a high degree of correlation existed between desire and contraction of the bladder.

A related study on pressure lines was carried on by Thompson,[105] who injected fluid under certain stated pressure, removed the catheter and later had the patients pass this. Under continuation of this plan with increasing amounts, he reported almost complete cure. It is interesting to note that he accompanied the procedure with demonstrations to the patients of the quantities that had been retained.

Position.—Lippmann [84] found that by placing the child in an extreme kyphotic position for one hour at the time of retiring, followed by emptying of the bladder, most children would remain dry during the night. This is based on the probability of stimulated renal activity under postural arrangement.

STATISTICAL SUMMARY

ENURETIC PATIENTS

Since the data obtained on these cases varied so widely, it has been necessary to present percentage figures in every case in terms of the total number in which information was obtained on the particular topic in question, and never in terms of the total series. The latter method would obviously be unfair and misleading.

Age, Color and Nationality.—The average age of the 108 boys was 9 years and 2 months; that of the 40 girls, 8 years. Seven boys and 5 girls were colored. Fifty-one boys and 24 girls were American, the main subdivisions for the remainder being as follows: Jewish, 11 and 5; Italian, 7 boys. This refers to the nationality of the parents.

Natal Conditions.—Of the 108 boys, in 10 instances legitimacy could not be determined; while of the remaining 98 children, 89 (89 per cent) were legitimate and 9 were not. Among the girls the facts were unknown in only 1 case; 37 were legitimate and 2 were not. Thus the total illegitimate group numbered 11, or 8 per cent of the known members.

The term was determinable in eighty-five of the males and in all of the females. Of these, the full-term infants constituted seventy-eight and thirty-eight, respectively, leaving seven boys and two girls as variants (7 per cent of group). These variants are as follows:

Male		Female	
7 months	4	7¾ months	1
8½ months	2	8½ months	1
10½ months	1		

With certain data indeterminate, it is observed that the character of the birth was known in 85 boys and 39 girls. Nine males and 5 females were delivered instrumentally; 2 boys were delivered by cesarean section. Thus of the 124 concerning which the facts were known, 16 (13 per cent) were not spontaneous deliveries.

Postnatal Conditions.—Twenty males and ten females were merely noted as having been breast fed; thirty-four additional males and sixteen additional females received this feeding for an average of eight months. Ten boys and five girls were never fed at the breast, making fifteen cases (16 per cent) in which an entirely negative history in this respect is forthcoming.

The average age of dentition of twenty-seven males for whom definite figures were obtained was 8½ months; of thirteen females, 6½ months. Thirty boys and thirteen girls were listed as "normal," one each as slow and the remainder as uncertain.

The average age at which forty-nine males began to walk was 14 months; of seventeen females, 12 months; twenty-two and ten, respectively, were "normal;" one of each sex was "slow." The average age of thirty-six males was 17 months; of seventeen females, 13 months.

Based upon the criterion of the examiners' judgment as to the degree of physical impairment, the following figures are listed:

	Male	Female
Normal	35	16
Slight impairment	41	10
Moderate impairment	25	10
Definite impairment	7	3

Thus, 35 per cent were of satisfactory physical condition, while 35 per cent more had but slight evidences of physical impairment. In the remaining 30 per cent, a considerable degree of physical underparity existed, sufficient to cause attention to focus on this as a possible cause per se.

One interesting phase of the physical condition is the height-weight ratio. Fifty-eight boys and seventeen girls (approximately 50 per cent of the whole) were in close approximation of this normal ratio. Forty boys and twenty-one girls averaged 8 and 7 per cent, respectively, underweight; eight boys and two girls averaged 10 per cent overweight.

An interesting sideline among the boys is the frequency of circumcision. Of eighty-three concerning whom the facts were known, sixty-three (76 per cent) had been circumcised; of eighty, ten (12 per cent) had undescended testes.

For only thirty-five boys and twenty-one girls were there sufficient data on illness for judgment. Nine boys and seven girls (30 per cent)

of this group had had definite nutritional problems; five and one, respectively, had had infantile convulsions (10 per cent).

Mental Status; General Characteristics.—The average for seventy-seven boys was an intelligence quotient of 88; for thirty-two girls it was 95, showing nearly average mentality for the group. Thirteen additional children might be considered normal; two were obviously superior, and ten were subnormal. When it is borne in mind that these figures include several children of very low intellect, in whom enuresis was a distinctly secondary problem to general trainability, it is to be noted that the enuretic child is an average child mentally.

Among eighty-seven concerning whom this fact was known, seventy-six were right-handed (87 per cent; forty-seven boys and twenty-nine girls) and eleven were left-handed (13 per cent; six boys and five girls).

Tantrums were manifested in forty-eight of sixty-three boys concerning whom there was certain information (76 per cent), and in sixteen of twenty-seven girls (60 per cent).

Thumbsucking was manifest in fifteen of forty-two boys (36 per cent) and in eight of twenty-two girls (36 per cent).

Nailbiting occurred in sixteen of thirty-nine boys (41 per cent) and in seventeen of twenty-five girls (68 per cent), a noticeable sex difference.

Thirty-nine of sixty boys (65 per cent) and eight of twenty-six girls (30 per cent) manifested the auto-erotic practice of masturbation, again an apparently sex-linked habit in part. Fifteen of fifty-five boys (27 per cent) and nine girls (25 per cent) gave some positive history of sex play.

Thirty of 101 boys gave a history of truancy as a part of the problem (30 per cent), but it is obvious that since many children of the series were under school age, the percentage is considerably higher. Only 3 of 37 girls (8 per cent) gave a similar history. Thirty-one of 95 boys (33 per cent) were reported as having stolen articles; 9 of 38 girls (23 per cent) were in a similar class.

Fifty-four of seventy-four boys (70 per cent) and twelve of twenty six girls (46 per cent) might be clearly classed as timid or fearful. This means that 66 per cent of the entire group, when suitable judgment could be made, might be so considered. Sixty-eight of eighty-two boys (83 per cent) and eighteen of twenty-seven girls (67 per cent) were considered as falling in the sensitive category. Obviously a part of this is result rather than cause; nevertheless, it is of some significance, when such a large percentage is encountered. Twenty-three of forty-eight boys and twenty-two of twenty-eight girls were characterized as to some degree aggressive; this constitutes 60 per cent of the total. Thirty-one

of fifty-seven boys and thirteen of twenty-one girls (or 56 per cent of all) were felt to be moderately good mixers (gregarious). All those who are not noticeably seclusive were included in this positive group.

Twenty-five of thirty-nine boys and thirteen of twenty-five girls (60 per cent of total) gave some rather obvious manifestation of jealousy.

One encounters a high percentage of infantilism—fifty-two of sixty boys (86 per cent) and twenty-four of thirty girls (80 per cent), a total of 83 per cent. What constitutes the criteria of infantile characteristics is discussed elsewhere.

Fifty-nine of seventy-one boys and fifteen of twenty-eight girls were believed to merit the descriptive term, "temperamental," a total of 75 per cent.

Fifty-three per cent of fifty-five boys and 45 per cent of twenty-two girls were deep sleepers.

Influence of Home Life.—Parental maladjustment was found in the cases of forty-eight of seventy-nine males and in twenty-two of thirty-five females, or 61 per cent.

Habit training was considered obviously at fault in sixty-eight of seventy-eight boys, and in twenty-nine of thirty-three girls, constituting 87 per cent of the group as a whole.

Nine of the boys had previously been institutional residents; twenty-one others were in institutions at the time of study. Two girls had been and five others were in institutions at the time of study.

Twelve boys and six girls had lived in foster-homes; concerning eleven boys adequate information was unavailable.

It was known that sixteen of ninety-five boys and five of thirty-eight girls had a step-parent. These figures were almost even as to step-fathers and step-mothers.

The economic status was poor in eighty, fair in fifty and good in eighteen cases.

Type, Frequency, Onset and Status of Enuresis.—The type was as follows:

	Males		Females	
Nocturnal	82	76%	35	87%
Diurnal	2	2%	2	5%
Nocturnal and diurnal	15	14%	2	5%
Enuresis and soiling	9	8%	1	2%

In the known and estimated cases, the frequency average was five times a week, with twenty-seven boys and seven girls yielding indeterminate information.

In eighty-three of the ninety-nine boys concerning whom this fact was known (84 per cent), and in thirty-three of the girls (80 per cent)

the onset occurred in infancy. The age at onset and the remainder was as follows:

	Males	Females
15 months	1	
2-6 months		1
3 years	2	
3-6 years	1	
4 years		1
4-6	1	1
5 years	2	1
5-6		1
6 years	2	
7 years	2	
7-6 years	1	
8 years	2	
9 years	2	
9-6 years		1
12 years		12

	Males	Females
Cured	24 22%	10 25%
Definitely improved	36 34%	14 35%
Not reported	14 13%	.. ....
No change	16 14%	7 18%
Indeterminate	18 17%	9 22%

Cured	23%
Improved	34%
No change	15%
Indeterminate	28%

Relation to Siblings and Other Members of the Family.—The status of the siblings was as follows:

	Males	Females
Only child	12	9
1 sibling	24	9
2 siblings	24	5
3 siblings	12	5
4 siblings	5	3
5 siblings	4	3
6 siblings	4	1
7 siblings	2	1
8 siblings	1	
9 siblings		1
12 siblings	1	
Unknown	19	4

A more or less obvious relationship of malbehavior to other children in the family was noted in thirty-five of sixty-two boys and in eight of nineteen girls. This is approximately one half of the total in which this factor could be estimated.

There was a positive relationship to other members of the family in thirteen of fifty-seven boys and in sixteen of thirty girls, or approxi-

mately in one third of the group concerning whom this was known. Since in most cases the preceding tabulation yields the information on the family member in question, it is not included here.

Conditioning Factors.—In those cases in which enuresis commenced after a dry interval, an attempt was made to determine what, if any, conditioning factors might be blamed. In twelve boys and four girls it was believed that some such factors were discoverable. Feelings of inferiority could be reasonably predicated in fifty-three of fifty-six boys and in twelve of seventeen girls, or in about 90 per cent.

ORGANIC CONTROLS

It was believed that something of value might be obtained by the comparative study of a small group presenting neurologic or psychiatric conditions in whom, however, enuresis was not a symptom. If these children did not have enuresis, some evidence at least would be set forth that the pathologic conditions in question were not etiologic with respect to enuresis.

Age, Color and Nationality.—This group consists of twelve children, six boys and six girls, averaging in age 8 years and 10 months (8 to 11 for the boys and 8 to 9 for the girls). All cases entered the outpatient department of the Orthopaedic Hospital and Infirmary for Nervous Disease, in the service of Dr. T. H. Weisenburg. All of the children were white and of American parentage, except one girl of Jewish parents. The maladies affecting them were diagnosed as follows: chorea, five; petit mal, one; hemiparesis, one; paraplegia, one; muscular dystrophy, one, and psychoneurosis, three.

Natal Conditions.—All were legitimately born children; eleven were full term, with one reported as a seven months' breech delivery. One was born after cesarean section and two after instrumental delivery.

Postnatal Conditions.—Five were reported as being breast fed, without specification of the duration of this feeding; three others averaged eight months, while one was never breast fed and for three the period was indeterminate.

Dentition was normal in six children; it began at 11 months in one, and was undetermined in five. Walking was reported at a normal age in eight cases, late in one and at 4 years in one. Talking was begun at a normal age in five cases, late in one and at an average of 13 months in three. The height-weight ratio was normal in eight, plus 10 per cent in one and averaged —7 in three.

Mental Status; General Characteristics.—The intelligence quotient was considered normal or superior in eight; it averaged 93 in four others on whom Binet's tests were performed.

All of the twelve children were right-handed.

Tantrums were present in two and absent in four. Nailbiting was present in six and absent in two. Masturbation and sex play were not positively determined in any, and were reported as absent in eight and ten cases, respectively. Truancy and stealing were uniformly negative.

Four children were viewed by their parents as being more than normally fearful; six were spoken of as sensitive; seven were characterized as aggressive, none as jealous and eight as good mixers. Four might be viewed as infantile on certain of the bases already considered, and four were listed as temperamental.

Only one was believed to be a deep sleeper, while five were definitely stated not to be such.

The Influence of Home Life.—The economic positions of the families could be fairly classed as poor in five and fair in seven. Three were only children; six had one or more known siblings. Parental maladjustment could be fairly assumed in only three; in three cases, habit training in general could be clearly seen to be at fault.

None of the children had lived in institutions, none had step-parents and none had lived in foster-homes. In two cases some stress in relations with siblings was evident. The average age of ceasing enuresis was 3 years and 1 month, with a minimum of 7 months and a maximum of 7 years.

As one studies this group, certain observations are of great interest. Physically, enuresis might easily be understandable; data on birth and development do not vary greatly from those of the enuretic series while habits are not differentially illuminating.

NORMAL CONTROLS

Age.—In this control group the average age of the individual child was 5 years and 7 months, the boys averaging 4 years and 10 months and the girls, 6 years and 4 months.

Natal Conditions.—Twenty-two of the males were full-term infants; two were born at 8½ months and one at 8. Twenty-three of the females were full-term infants; one was born at 8 months and one was reported born one week after the full period of gestation. This gives forty-five, or 90 per cent, as full-term children and the entire number within the one month deviation.

Birth was normal in seventeen of the boys, instrumental in seven and a breech presentation in one. Among the girls there were nineteen normal and five instrumental deliveries; one occurred by cesarean section. Thus, thirty-six, or 72 per cent, deliveries were normal and twelve, or 24 per cent, instrumental.

Postnatal Conditions.—Twenty-two of the boys were breast fed for a longer or shorter period, averaging five and seven-tenths months. Among the girls, twenty-three averaged six months of breast feeding. When bottle feeding was figured, it was felt best to designate it in terms of total age attained, which is, of course, what actually is shown in the figures on breast feeding. Twenty-one males who were bottle fed averaged fourteen months at weaning, three were not given the bottle, and in one the period was undetermined. Among the females, eighteen averaged the same age—14 months—as the age of deprivation of the infantile mode of eating; four were not given the bottle, and in three the period was undetermined. Thirty-nine (78 per cent) averaged 14 months as the weaning age.

Among twenty-five males the average age of dentition was 8 months, a figure almost identical with that for the twenty-four females for whom a definite figure was ascertained. The average age of talking for twenty-one males was 16 months, and for twenty-five females 13 months, a total average of just over 14 months.

The average age of walking for the two groups was within a fraction of the same figure, 13 months.

At the time the data were gathered, thirty-four (68 per cent) of the children were considered as essentially normal in height and weight (eighteen males and sixteen females). Four boys averaged 8 per cent overweight and four averaged 8 per cent underweight. Four girls averaged over 8 per cent, while five averaged over 7 per cent. When one considers that the variation up to 7 per cent is often regarded as within normal limits, the entire group may be viewed as normal in this respect.

Twenty-four of the boys were reported as essentially normal physically; one had a mild cardiac valvular lesion. Twenty of the girls were thoroughly normal physically, with slight deviations in four and a persistent asthma-eczema difficulty in one. It may be significant that the last child is one in whom enuresis persisted far past the usual time.

One would expect practically every child to have had such frequent maladies as colds and the commoner children's diseases. Such was the case; that three boys and eight girls were reported as having had no illness is worthy of specific mention. From this point of view, the finding of one third of the girls thus so singularly free from illness is interesting. Pyelitis ranges high among the girls, nine of the twenty-five having had this disease. One boy and two girls were listed as having had nutritional disturbances as infants; one boy had convulsions.

Mental Status.—Seven boys and eleven girls in whom intelligence quotients were determined averaged within a fraction of the same figure, 126. Since this is in the definitely superior group, it is strong evidence

of the mental status of over one third of the group. Since I know personally all but ten of the group, and know of these ten from authoritative sources other than the parents, it may be stated with finality that the intelligence in every case is of at least normal degree and in almost every one, definitely above the average.

Seventeen males and seventeen females (68 per cent) were reported as primarily right-handed. One male and three females were left-handed, while seven males and five females were reported as primarily ambidextrous. Such a figure as 24 per cent of ambidexterity is at least evidential toward the view of the early similarity of the hemispheres.

Commencement of Excretory Control.—The average age at attempting some control of the bowel among twenty-four boys was 7 months; among twenty-two girls it was 6½ months. Good results were obtained, except occasional accidents, at the age of 15 months among the boys and at the age of 13 months among the girls.

Constructive attempts to inculcate regularity in daytime control of the bladder were made at 11 months, the average age of twenty-five boys, and at 8 months, the average age of twenty-two girls. Definite results were reported at 14½ months among the boys and at 11 months among the girls. At the age of 19 months among the boys and of 15 months among the girls, day wetting of the clothes ceased, except for accidents. One case is of especial interest. The mother, following a definite idea, and in spite of the contrary advice of friends, made no attempt at any training until the child was 23½ months. Then within a few days both day and night wetting ceased permanently.

Among eighteen males the average age of commencing control training was 16½ months, while among twenty-one females it was 11½ months. Results were noted at 18½ and 15 months, respectively. Bed-wetting ceased at 23 months among the boys and at 22 months among the girls. This incidence can be seen so readily from the tabulations, the individual figures indicating minimum and maximum ages, that it seems useless repetition to point them out here. However, one case (XL) deserves special comment. This girl, an unusually mature child, both emotionally and intellectually, suffered from enuresis until about the age of 10 years. The close association with an eczematous and asthmatic condition seems probable. She has been included here for many reasons, although the persistent enuresis would seemingly have ruled her out. Her age, however, is not figured among the totals in the matter of training against enuresis. It is thus to be noted that the girls appear to be consistently younger at any given stage of habit development than are the boys. One must bear in mind, nevertheless, a widespread tendency to show a little more unconscious memory favoritism to the girls in all such matters when a child comes in for criticism. On the other hand, it

is not at all improbable that such an attitude, if not carried to the destructive point, may actually impress on female children earlier the necessity for such control.

Breaks due to illness occurred in fourteen boys and five girls (a total of 38 per cent). Relapses of definite character and not directly attributable to illness were experienced in eight boys and ten girls (36 per cent).

Sleep.—In ten males and eleven females (42 per cent) control of bedwetting was accomplished by sleeping through the night. This should be a fair answer to the frequently voiced point that the infantile bladder is too small to accommodate itself to the night's secretion of urine. For these nights averaged eleven and a half hours in bed. Nine other children (six boys and three girls) awakened when it was necessary to visit the bathroom, while eighteen (36 per cent) of the combined group had to be awakened by the parent or nurse.

Sixteen males and ten females (52 per cent of all) were listed as deep sleepers, seven males and thirteen females (40 per cent in all) as normal and two of each subgroup (8 per cent in all) as light sleepers.

Twenty boys and twenty-one girls were listed as not restless at night (82 per cent of total) and only five and four, respectively, or 18 per cent, as restless.

It has here been thought advisable to classify the cases into groups of children who slept in a separate bed and room from the parents and those who slept merely in a separate bed in the same room. These are designated "class *A*" and "class *B*," respectively. Eleven boys and fourteen girls comprise the first group; fourteen boys and eleven girls, the second. Thus, for the group as a whole, the division is even.

Naps were being taken by forty-seven of the total number (by all but two boys and one girl) at the time of training. These naps were more or less often accompanied by enuresis in nine of the boys and ten of the girls (38 per cent of total), while for four additional children insufficient data were obtained to allow classification. In spite of this high incidence of wet naps, however, in only one of each sex was any relationship noted between such wet naps and the occurrence of enuresis during the night following. In both these instances it was believed that a lessened tendency to enuresis occurred at such times.

Without detailed studies and special psychoanalytic investigations, it is well recognized that dream studies in small children are relatively valueless. In the majority, naturally, enuresis is controlled before the reported occurrence of much dreaming; nevertheless, a total of eight (five boys and three girls) had such dreams. Nineteen boys and eighteen girls (74 per cent of all) gave a negative history for dreams.

Of more specific interest is the occurrence in two cases (one boy and one girl) of dreams of urination. These are frequently recounted by adults as having occurred in their childhood, wherein the individual sees himself in a perfectly suitable place for micturition and awakens to find the bed wet. No less than seven of my friends, with whom I have discussed the problem of enuresis, have reported this phenomenon in themselves.

Treatment.—It is obvious that in the attempts to control bedwetting, awakening of the child is the first and most frequently used remedy. Hence some study was made of this topic with reference as to who did the awakening. The father functioned as the awakener in three cases (one boy and two girls), the mother in four, both parents in thirteen (eight and five) and the nurse or maid in two (both girls), with inadequate information in five. As for the others, in six the child always slept through the night, while in seven (three boys and four girls), when awakening did happen for purposes of micturition, it was by the child himself.

In only one case (XI.) was an alarm clock used, that of the girl who acquired control very late. It was believed to have been a very definite factor in success here, since it was tried by the parents on the basis of suggestion by a letter from me. The absence of such a method is not to be wondered at in a group in which control was secured relatively easy and early.

A physician was consulted for the trouble in ten cases (five patients of each sex). Perhaps this incidence would have been higher had there not been such a high incidence of physicians among the parents. However, this factor may operate in the other direction, in that families of physicians may be more likely to seek professional advice.

Drugs were used in only two cases (both patients were girls). One of these was the previously mentioned girl who was very late in acquiring the full control. In neither case was the drug—in both cases atropine—believed to have been of any benefit.

Influencing Factors.—The matter of discussion between the parents in the child's presence can obviously serve to impress the child with the seriousness of the "offense," or as an aid in the sense of affording the child a conviction of the interest and assistance of the father. Unfortunately, the former is what usually occurs. In the case of nine boys and four girls (*26* per cent of the total) this happened, most of the children gaining control early enough to avoid much exposure to this potential detriment.

To some degree fondling is reported in thirty-one (*62* per cent) of the total number of cases—sixteen boys and fifteen girls. It is reported as definitely not having been indulged in in seventeen of the cases.

The widespread belief in the greater frequency of enuresis in the winter months finds justification in this study, wherein twelve boys and fifteen girls (54 per cent) gave clearcut histories of increased trouble in the winter or during sudden lowering of the temperature.

Approximately one-fifth (six boys and five girls) were believed to have been assisted in the securing of control by conscious attempts on the parent's part in lengthening the intervals between urination during the day. Five additional cases were not classifiable, while thirty-five of the total number either showed no response to this attempt or, what usually was the case, made no endeavor in this direction.

As far as ingestion of fluid is concerned, almost equal numbers are reported on the positive and the negative side, twelve boys and eleven girls showing the influence of the lessened ingestion of liquid.

In a few instances definite alterations in behavior toward one or both parents occurred (two boys and four girls). In a few it was the development of antagonism toward a parent; in the remainder, it was at least a commencement of the break of extreme dependence of babyhood.

Teasing by other children in the family was reported in the cases of two boys and four girls; by outsiders, only in the instance of one girl. Thus the painful experience of shaming, so difficult for the usual enuretic child, was hardly a factor of consequence in this group.

In only one boy and two girls was any disturbing factor, such as of other residents in the household, believed to be a real influence. Thus the presence of a colored nurse in one instance, who refused in effect to cooperate with the mother's attempts at training, was a handicap for some time.

On the other hand, thirteen cases (eight boys and five girls) reported certain definite events, procedures or happenings which exerted a marked and even a dramatic effect on the enuresis. Removal of diapers with or without replacement by panties exerted such an effect in seven instances. As the parents give the account of these things one cannot but be impressed with the importance of such recognitions of the "growing up" process. It is also noted from the chart that in the case of two boys permission to accompany father to the bathroom and stand to urinate "just like daddy" exerted a definite therapeutic effect.

However, under this heading of conditioning factors comes one instance of a negative character. This boy (XXI), who was accustomed to awaken himself and walk to the bathroom, one night struck his head on an article of furniture, which induced a fear of the dark sufficient to cause the reappearance of enuresis for some time.

Habits and Personality.—When consideration is given to these phases of the problem, one admittedly enters the sphere in which opinion necessarily tends to replace the greater objectivity of much of the previously

discussed material. Nevertheless, considerable reliance must be placed on these factors. I know these children to a considerable extent, and I feel that the personality traits are as accurately listed as is possible. After all, no one can pass with more authority on the traits and habits of small children than intelligent parents, at least so long as one is not given observational playroom facilities.

Thirteen boys and twenty-one girls were considered to have shown clearcut tantrums during the training period. This is 68 per cent of the total, and may well indicate the normality of such behavior in the striving for self-assertion. One may wonder at the apparent sex difference here.

Crying is a harder thing to determine, perhaps since what is meant is an undue or unusual amount. This has been reported for nine boys and twenty-one girls, and it is probably but another expression of the tantrum reaction.

Seven boys and nine girls (32 per cent of total) presented thumb-sucking as a habit during the training period.

For only two patients, both boys, is masturbation reported. While this appears to be a low figure, it must be remembered that this habit usually becomes a problem at an age somewhat more advanced than that in which normal control of the bladder is being obtained. For one boy and one girl no report was made on this topic.

(To be Continued)

Pediatric Biographies

WILLIAM HEBERDEN, THE ELDER

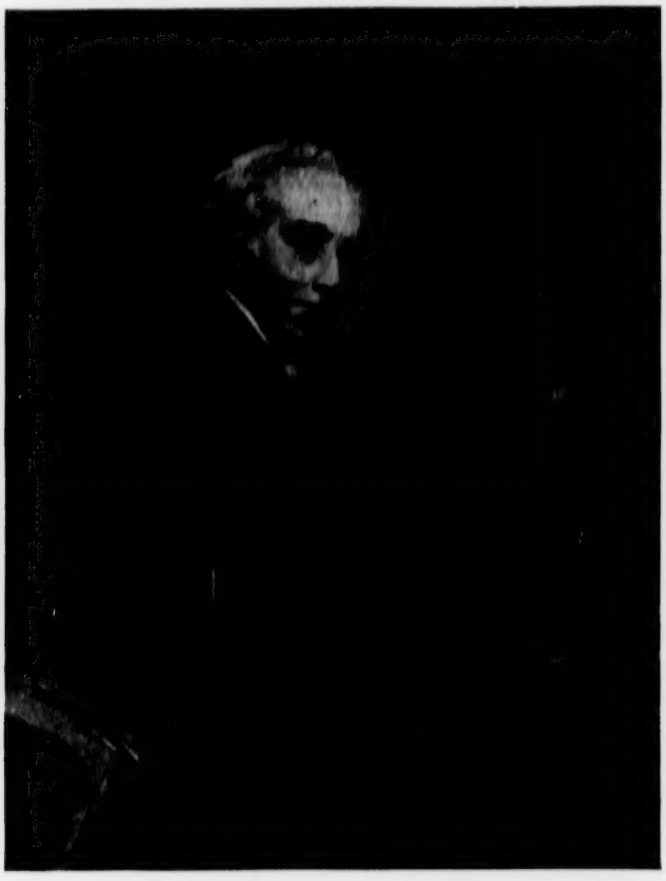
1710–1801

JOHN RUHRÄH, M.D.
BALTIMORE

Heberden was born a year before Cadogan, and, like him, made a definite and lasting impression on the medical thought and practice of his time. He was a native of London and was educated at the grammar school in Saint Saviour's Churchyard, Southward, from which he transferred to St. John's College, Cambridge, in 1724, as the Roll of the Royal College of Physicians states, "at an unusually early age." He was elected a fellow in 1730, and received the A.B. degree in 1728, A.M. in 1732 and M.D. in 1739. For some years he practiced medicine in Cambridge, where for ten years he read an annual course of lectures on materia medica. His collection of specimens, which he used to illustrate his lectures, was presented to the university in 1750. He was made a Fellow of the Royal College of Physicians in 1746, a member of the Royal Society in 1749 and an honorary member of the Royal Society of Medicine in Paris in 1778. He was a popular member of the college, as is attested by the fact that he was Goulstonian lecturer in 1760. He was censor in 1749, 1755 and 1760, Consiliarius in 1762 and was constituted an Elect in 1762, which office he held until 1781. He retired about this time to Windsor for the summer months, but continued his practice in London in the winter. He died at his house in Pall Mall in 1801, and is buried in the church in Windsor, where there is a tablet with the following inscription:

Near this place are deposited the remains of
William Heberden, M.D.
who died the 17th May, 1801,
in the 91st year of his age.
He practiced physic,
first at Cambridge, afterwards in London,
with great and unsullied reputation above 50 years.
His distinguished learning,
his sweetness of manners, and active benevolence
raised him to an uncommon height in public esteem:
above all, his deep sense of religion,
which he cultivated with unremitting attention,
regulated his conduct through a long and busy life,
and supported him to the last
with unabated cheerfulness and resignation.
His widow and three surviving children erected this
tablet to his memory.

Epitaphs are rarely true statements, but this one is a statement of the truth about Heberden, and it was much amplified by many of his contemporaries in their praise of him. His son gave an incomparable eulogy in his Harveian oration for 1809. There is a book on the life of Heberden by A. C. Buller, and McMichael has some charming lines



WILLIAM HEBERDEN
1710-1801

about him in "The Gold Headed Cane" in which the well known incident concerning the widow of Dr. Conyers Middleton is related. After the death of her husband, she came with a manuscript on the inefficacy of prayer which she wished to publish. Rather than see it in print, Heberden ascertained that a publisher was willing to pay £150 for it. He then gave the widow £200 and burnt the manuscript.

Heberden was a gentleman of the old school and a rare scholar. He wrote a Latin so fine in quality that Dr. Johnson called him ultimus Romanorum (the last of the Romans), and his commentaries appeared in Latin Medical Classics published at Leipzig by Friedländer. Soemmering, who brought out his works in Germany, called him medicus vere Hippocrates.

Heberden made a number of contributions to medicine, and he was largely responsible for the reform of the London Pharmacopeia which up to his time included most objectionable products, more remarkable if possible than those recommended by some of the advertisements of gland products of the present day. His satirical pamphlet, "Antitheriaka, an Essay on Mithridatum and Theriaca," actually laughed the nonsensical and absurd out of the pharmacopeia.

He was responsible for the Medical Transactions of the Royal College of Physicians, which were issued in three volumes. These contain sixteen papers by him. He wrote on influenza and on the pulse. In 1766, he published a paper on angina pectoris, and it came to be called "angina heberdenii." The next year he described night blindness and the nodes on the fingers, which he called digitorum nodi, but which now bear his name.

His Commentaries were arranged in 1802, in both Latin and English, but they were not published until a year after his death, when the volume was published by his son with the title "Commentarii de morborum historia et curatione." Every young practitioner should read this book, and it will not hurt the older ones. It contains, among other things, a good description of chickenpox, which appears herewith. His short description is as follows:

1. The appearance for the second to the third day from the eruption of that vesicle full of serum upon the top of this pock. 2. The crust, which covers the pocks on the fifth day; at which time those of the small-pox are not at the height of their suppuration.

He paid especial attention to diseases of children, and the little book by his son to be noticed later was unquestionably much influenced by his observations and views.

VARIOLAE PUSILLAE. THE CHICKEN-POX.

The chicken-pox and swine-pox differ, I believe, only in name: they occasion so little danger or trouble to the patients, that physicians are seldom sent for to them, and have therefore very few opportunities of seeing this distemper. Hence it happens that the name of it is met with in very few books, and hardly any pretend to say a word of its history.

But though it be so insignificant an illness, that an acquaintance with it is not of much use for its own sake, yet it is of importance on account of the small-pox,

with which it may otherwise be confounded, and so deceive the persons, who have had it, in a false security, which may prevent them either from keeping out of the way of the small-pox, or from being inoculated. For this reason I have judged it might be useful to contribute, what I have learned from experience, towards its description.

These pocks break out in many without any illness or previous sign: in others they are preceded by a little degree of chillness, lassitude, cough, broken sleep, wandering pains, loss of appetite, and feverishness for three days.

In some patients I have observed them to make their first appearance on the back, but this perhaps is not constant. Most of them are of the common size of the small-pox but some are less. I never saw them confluent, nor very numerous. The greatest number, which I ever observed, was about twelve in the face, and two hundred over the rest of the body.

On the first day of the eruption they are reddish. On the second day there is at the top of most of them a very small bladder, about the size of a millet-seed. This is sometimes full of a watery and colourless, sometimes of a yellowish liquor, contained between the cuticle and skin. On the second, or, at the farthest, on the third day from the beginning of the eruption, as many of these pocks, as are not broken, seem arrived at their full maturity; and those which are fullest of that yellow liquor, very much resemble what the genuine small-pox are on the fifth or sixth day, especially where there happens to be a larger space than ordinary occupied by the extravasated serum. It happens to most of them, either on the first day that this little bladder arises, or on the day after, that its tender cuticle is burst by the accidental rubbing of the clothes, or by the patient's hands to allay the itching which attends this eruption. A thin scab is then formed at the top of the pock, and the swelling of the other part abates, without its ever being turned into pus, as it is in the small-pox. Some few escape being burst; and the little drop of liquor contained in the vesicle at the top of them grows yellow and thick, and dries into a scab. On the fifth day of the eruption they are almost all dried and covered with a slight crust. The inflammation of these pocks is very small, and the contents of them do not seem to be owing to suppuration, as in the small-pox, but rather to what is extravasated immediately under the cuticle by the serous vessels of the skin, as in a common blister. No wonder therefore that this liquor appears so soon as on the second day, and that upon the cuticle being broken it is presently succeeded by a slight scab: hence too, as the true skin is so little affected, no mark or scar is likely to be left, unless in one or two pocks, where, either by being accidentally much fretted, or by some extraordinary sharpness of the contents, a little ulcer is formed in the skin.

The patients scarce suffer anything throughout the whole progress of this illness, except some languidness of strength and spirits and appetite, all of which may probably be owing to the confining of themselves to their chamber. I saw two children ill of the chicken-pox, whose mother chose to be with them, though she had never had this illness. Upon the eighth or ninth day after the pocks were at their height in the children, the mother fell ill of this distemper then beginning to shew itself. In this instance the infection lay in the body much about the same time that it is known to do in the small-pox.

Remedies are not likely to be much wanted in a disease attended with hardly any inconvenience, and which in so short a time is certainly cured of itself.

The principal marks, by which the chicken-pox may be distinguished from the small-pox are,

1. The appearance on the second or third day from the eruption of that vesicle full of serum upon the top of the pock.

2. The crust, which covers the pocks on the fifth day; at which time those of the small-pox are not at the height of their suppuration.

Foreign medical writers hardly ever mention the name of this distemper; and the writers of our own country scarce mention anything more of it, than in name. Morton speaks of it as if he supposed it to be a very mild genuine small-pox. But these two distempers are surely totally different from one another, not only on account of their different appearances above mentioned, but because those, who have had the small-pox, are capable of being infected with the chicken-pox; but those, who have once had the chicken-pox, are not capable of having it again, though to such as have never had this distemper, it seems as infectious as the small-pox. I wetted a thread in the most concocted pus-like liquor of the chicken-pox, which I could find; and after making a slight incision, it was confined upon the arm of one who had formerly had it; the little wound healed up immediately, and shewed no signs of an infection. From the great similitude between the two distempers, it is probable, that, instead of the small-pox, some persons have been inoculated from the chicken-pox, and that the distemper which has succeeded, has been mistaken for the small-pox by hasty and unexperienced observers.

News and Comment

GENERAL

Resolution on the Death of Dr. Harry M. McClanahan.—The Section on Diseases of Children, convened at the Eighty-First Annual Session of the American Medical Association in Detroit, June 23, 1930, learned with profound sorrow of the death of Dr. Harry M. McClanahan on Nov. 29, 1929.

Dr. McClanahan was an honored and beloved member of the Section. He enjoyed a wide acquaintance and was held in the highest esteem. He was chairman of the Section in 1901 and represented it in the House of Delegates during the 1915 and 1916 sessions.

His quiet, gentle manner, with a genuine spirit of friendship, keen quest of knowledge and a love for truth, endeared him to a host of colleagues through the passing years. The members of this section who knew him and loved him will miss his kindly presence.

The Section on Diseases of Children inscribes his name on the honor roll of those who served American pediatrics creditably, long and faithfully, records in its minutes an expression of sorrow on the death of Dr. McClanahan and recommends that a copy of this resolution be transmitted to his family.

SOCIETY NEWS

Italian Pediatric Society.—The Piedmont Section of the Italian Pediatric Society (Sezione Piemontese della Società Italiana di Pediatria) at its meeting on April 8, 1930, after a prolonged presentation of data on the value of antidiphtheritic vaccination as a means to reduce the incidence of this disease, and after due consideration of this data, resolved to recommend the widespread use of the procedure in all children in the Kingdom of Italy. It also recommended the launching of a general propaganda in the schools and among the general public as to the great value of this prophylactic measure on the part of physicians and teachers. The Society favored the adoption in the near future, of obligatory antidiphtheritic vaccination.

Abstracts from Current Literature

Pathology, Bacteriology and Biochemistry

THE EFFECT OF PARATHORMONE ON NORMAL AND VITAMIN B-DEFICIENT RATS. W. B. ROSE and C. J. STUCKY, Am. J. Physiol. **91**:513, 1930.

Because of a number of similarities in behavior in dogs suffering from parathyroid tetany and from deficiency in vitamin B, the hormone was tested for possible content of the vitamin complex. Using rats in which to a diet deficient in vitamin B was added a parathormone-dextrose preparation prepared in such a way as to preserve any vitamin B that may have been originally present, or with some animals, supplementing the deficiency by daily subcutaneous injection of parathormone, it was found that the hormone was without effect in overcoming the vitamin deficiency. Old rats succumbed after the third injection of 25 units of the hormone. Young rats, on the other hand, survived four successive injections of a proportional dosage. The injections resulted in a rise of blood calcium by approximately 40 per cent.

EGGERS, Omaha.

EFFECTS OF PARATHYROID INSUFFICIENCY. J. N. ESAU and O. O. STOLAND, Am. J. Physiol. **92**:1, 25 and 35, 1930.

In three articles dealing with the subject of parathyroid insufficiency, the writers report, in dogs, the following observations: An increase of inorganic phosphorus in the blood, with an increase of the total acid-soluble phosphorus which accompanied in amount the severity of the symptoms. However, in cases with mild symptoms of parathyroid deficiency with delayed onset, the blood phosphorus usually fell below normal. Low inorganic phosphorus in the blood, and particularly a low content of acid-soluble phosphorus, were highly favorable to recovery. Magnesium lactate and morphine sulphate were found to have beneficial effects despite a secondary progressive rise in inorganic and acid-soluble phosphorus, presumably through depressant action on the respiratory center and other nervous mechanisms. No relationship could be established between rate of fall of blood calcium and the type and severity of symptoms, although there was evidence of a relation to time of onset. The behavior of the calcium and acid-soluble phosphorus compounds in the blood of parathyroidectomized dogs is attributed to a disturbance of phosphocreatine metabolism chiefly within the muscle fibers, which affects the calcium-potassium ratio, with an effect on the permeability and irritability of the tissues whereby there is an accumulation of otherwise nontoxic metabolites with access of these to the cellular protoplasm, this producing the various clinical manifestations of parathyroid insufficiency. Administration of parathormone was found to reduce the inorganic and acid-soluble phosphorus until the calcium rose much above the normal. Then there was a rapid rise of inorganic phosphorus followed by a marked increase in acid-soluble phosphorus usually until death ensued. The injection of liver extract into dogs with parathyroid insufficiency was found to produce marked visceral symptoms, which were accompanied by increased severity of the tetany, or by the induction of a brief period of tetany in dogs during the depression state. Following the visceral reactions there was a recovery from the tetany; when these failed to develop, there was no improvement after treatment with extract. While in the unbenefited animals there was a rise of blood calcium following the injection of the liver extract, in animals suffering from tetany, and in normal animals, the injection was followed by a slight lowering of blood calcium. Synchronously, with the visceral reactions there was a marked fall in blood pressure, and during the period of low pressure there was distinct reduction of coagulation time.

The administration of the liver extract did not markedly prolong the recovery period of thyroparathyroidectomized animals. In general, liver extract was not found to be as effective an agent in counteracting the toxemia of parathyroid tetany as were calcium and other substances.

EGGERS, Omaha.

THE EXPERIMENTAL PRODUCTION OF XEROPHTHALMIA IN MICE. E. POMERENE and H. H. BEARD, Am. J. Physiol. **92**:282, 1930.

In mice fed on adequate diets containing casein, extracted (A and B free) casein, and edestin as the protein factor, and commercial crisco, or this aerated for sixteen hours at 140 F., it was found that commercial edestin contained no vitamin A, and while crisco contained enough of this vitamin to prevent xerophthalmia in mice, it was inadequate to protect rats in similar circumstances. The latter evidently require more of the antixerophthalmic factor than do mice.

EGGERS, Omaha.

THE RESISTANCE OF SCARLET FEVER STREPTOCOCCI TO THE ACTION OF BACTERIOPHAGE. JOHN E. WALKER, J. Infect. Dis. **45**:304, 1929.

Streptococci from erysipelas are in general susceptible to lysis by the streptococcus bacteriophage described by Shwartzman. Scarlet fever streptococci so far tested are resistant. It also appears that epidemic sore throat strains are susceptible to lysis when freshly isolated. Streptococci may lose their susceptibility to lysis on cultivation on artificial mediums. Other strains may retain their susceptibility even after ten years' cultivation. All nonhemolytic streptococci tested were resistant to the bacteriophage.

AUTHOR'S SUMMARY.

A STUDY OF CERTAIN HEMOLYTIC STREPTOCOCCI OF THE BETA TYPE IN CERTIFIED MILK. EDITH HAYNES, J. Infect. Dis. **45**:316, 1929.

The majority of hemolytic streptococci of beta type in certified milk which either do not hemolyze at all in fluid mediums, or do so only slightly, are members of group 7 according to the classification of Brown, Frost and Shaw. This group closely resembles *Str. mastitidis* (group 2) in cultural and biologic characteristics. Some of the strains found in certified milk which do not hemolyze in the test tube are members of group 9. This group is very similar to group 4 which does hemolyze in fluid mediums. Groups 7 and 9 differ in their fermentation of salicin and in their appearance on blood agar plates. Many of the strains of group 9 produce double or triple zones of hemolysis around the colonies. Strains belonging to group 8 are found infrequently. Strains of groups 7 and 9 usually do not hemolyze in fluid mediums, but this test is not constantly negative. The age of the inoculum and the age of the culture tested affect the hemolytic titer in the standard test only slightly, but an inherent quality in the culture probably is more often the source of variation. This test is, however, considered sufficiently reliable to use as a basis of classification. The slight tendency for the weakly hemolytic strains to show hemolysis in the tube indicates a close relationship between them and the strongly hemolytic strains. None of our cultures which had been kept on artificial mediums for some months proved pathogenic for mice. A narrow capsule may be present on young cultures of group 7. This is not so distinct or obvious as the capsule of *Str. epidemicus* (Davis) and does not persist so long. All the strains studied hydrolyze sodium hippurate. Growth of these strains in litmus milk is very similar to that of other streptococci which ferment lactose, and this test is of no differential value. A temperature of 58 C. for twenty minutes is sufficient to kill these strains in a lightly inoculated medium. They probably would not survive pasteurization unless present in milk in large numbers. Agglutination tests show a close serologic relationship between groups 2 and 7. Groups 3 and 4 do not seem to be so closely related to group 7. Group 7, to which most of our strains belong, seems from both a cultural and a serologic stand-

point to be a very homogeneous group. This group is distinguished from group 2 only by a weak hemolytic titer.

AUTHOR'S SUMMARY.

ON THE PURIFICATION AND CONCENTRATION OF SCARLET FEVER TOXIN. LAWRANCE E. SHINN, J. Infect. Dis. **46**:76, 1930.

The experiments reported here indicate that a lethal dose of scarlet fever toxin for rabbits has not been established. Although rabbits were given intravenous injections with more than seven times the dosage of scarlet fever toxin designated by Hartley as the lethal dose for rabbits, no specific lethal action of the toxin was demonstrated. It was possible to concentrate scarlet fever toxin by precipitation with sodium sulphate and acetic acid. Attempts to obtain further purification by fractional precipitation with sodium sulphate were unsuccessful. Attempts to concentrate scarlet fever toxin by precipitation with acetic acid alone were not successful. Precipitation with acidified alcohol gave the most uniform and the best results. Rabbits are not suitable for standardization of scarlet fever products. Concentration of scarlet fever toxin may be obtained by several methods. Of those used in these experiments, precipitation with alcohol acidified with acetic acid gave the best results.

AUTHOR'S SUMMARY.

RELATION OF PELLICLE FORMATION AND TOXICOGENICITY IN DIPHTHERIA CULTURES. RALPH H. HEEREN, J. Infect. Dis. **46**:161, 1930.

That a definite correlation exists between pellicle and toxicogenicity is shown by the fact that eighty-nine of the 100 toxicogenic colony cultures produced a definite and characteristic pellicle on Wadsworth's medium to which they had become habituated by means of a series of transfers carried over a forty-five day interval. That the pellicle is not necessary for formation of a strong toxin is shown by the fact that the remaining eleven of the 100 toxicogenic colony cultures, carried through the same growth and test conditions, were consistently apellicular. That the increase in toxicogenicity was due to habituation of the cultures to the medium rather than to increased degrees of pellicle formation is shown by the fact that the apellicular forms demonstrated increase similar to those of the pellicular forms. On the other hand it has been shown that pellicle formation in diphtheria cultures does not determine toxicity, since six of fifteen cultures (proved atoxicogenic by two methods) showed pellicles regularly.

AUTHOR'S SUMMARY.

THE HISTOGENY OF TERATOMA. G. W. NICHOLSON, J. Path. & Bact. **32**:365, 1929.

A retroperitoneal cystic tumor 11.5 by 8.5 by 5 cm. was found attached to the abdominal aorta, left kidney and left suprarenal gland of a 4 months old female child. Histologic derivatives of all germinal layers were demonstrable. The nervous elements were more abundant than the epidermis and its derivatives and ependyma, in places forming a choroid plexus, lined the major cavity. Of particular interest was a metanephros which was thought to be an inclusion of the upper reniculi of the child's left kidney, since the suprarenal gland was separated from this kidney by 4 cm. of tumor tissue and because only five pyramids were found in the left kidney.

RUKSTINAT, Chicago.

THE PATHOLOGICAL ACTION OF LIGHT. A. G. LEVY, J. Path. & Bact. **32**:387, 1929.

The essential action of white light on sensitized tissues and of ultraviolet light on nonsensitized tissues appears to be identical. The result of prolonged irradiation of the mouse's ear is an immediate complete stasis, with subsequent necrosis. The result of less prolonged irradiation is a delayed stasis, with sub-

sequent necrosis. In no case is stasis conditioned by the formation of clots. It is due to an inflammatory reaction, accompanied by extravasation of plasma from the vessels and consequent aggregation of corpuscles. The necrotic changes are a consequence of the cessation of circulation. The coagulation of extravasated plasma is a consequence of circulatory arrest. Hardening of the dead tissue is due to mechanical desiccation. Hypertrophy and infiltration of the epithelium are striking results of irradiation which is insufficient to produce general stasis. The hypertrophy is definitely shown to result from a brief period of irradiation.

AUTHOR'S SUMMARY.

PERISTALSIS IN THE SMALL INTESTINE. A. PEIPER, Jahrb. f. Kinderh. **129**:263 (Jan.) 1929.

Peiper states that in the upper portions of the small intestine distention causes peristalsis as soon as a definite critical pressure is reached. For the onset of peristalsis no strict law is demonstrable. The H-ion concentration and the lactic and acetic acid contents of the intestine caused no peristaltic irritation in the concentrations employed in the experiments. However, intestine affected with diarrhea was found to be more irritable and sensitive to chemical stimuli.

These results, obtained by investigation of the intestine in well infants, may be used to interpret conditions in the dyspeptic infant in whom there is a lowering of the threshold and an increase of the irritating substances in the intestine.

A. F. ABT, Chicago.

ISO-HEMAGGLUTININS IN INFANCY. A. A. BELJAJEW and J. A. TSCHEKALIN, Jahrb. f. Kinderh. **124**:88 (May) 1929.

Grouping of human blood is a congenital characteristic, although it is not fully completed till the end of the first year. In new-born infants with subnormal weights the percentage of nonspecific reactions is greater than in new-born infants of normal weight.

According to Beljajew and Tschekalin, the grouping percentage in the various races is about the same in childhood as in adult life. In 53.3 per cent of the cases the blood groups of mother and child were the same, most often in group 1, least often in group 4.

A. F. ABT, Chicago.

THE DIURETIC HORMONES IN THE BRAIN. J. OLIVET, München. med. Wchnschr. **77**:58 (Jan. 10) 1930.

Olivet found that experimental injury of the uvula of the cerebellum or the lateral aspect of the floor of the fourth ventricle of rabbits resulted in the appearance in the blood of a hormone that caused diuresis. He produced lesions in the brains of eleven rabbits and bled them twenty-four hours later. The protein-free serum was injected intravenously into other rabbits and the output of urine measured. One showed no effect; four showed a threefold increase in the excretion of urine, and six excreted from four to twenty times the amount of urine measured during a preliminary period of observation. The increase in excretion began ten minutes after the injection of the serum. The animals with the most marked polyuria also had glycosuria. Control animals given injections of the serum of rabbits whose brains had not been injured showed no change in urinary output.

BRAHDY, Mount Vernon, N. Y.

Nutrition

BREAST FEEDING. JESSE R. GERSTLEY, Arch. Pediat. **46**:749 (Dec.) 1929.

Over a period of seven months, two infants of one mother were weighed before and after nursing. The amounts taken at the individual nursings varied

greatly. As early as the fourth week one baby took as much as from 8¼ to 9 ounces (251 to 266 cc.) of breast milk. The amount of milk secured by the infants varied from one feeding to another and also day by day. Tables are given showing the milk obtained at the various feedings and the amount of gain in weight.

WILSON, Norfolk, Va.

THE IMMUNOLOGICAL SIGNIFICANCE OF COLOSTRUM. THEOBALD SMITH, J. Exper. Med. **51**:473, 1930.

The protective antibody content of normal cow serum is below that of colostrum of the same animal. The method used does not permit the titration of the actual amount of the antibody in serum. Quantities up to 2 cc. have no protective effect. The same limitations apply to the titration of milk owing to the introduction of large quantities of foreign protein into the peritoneal cavity of the guinea-pig. When cows were immunized and a serum of high titer obtained, the antibodies in the milk of such cows rose to within the range of the method of testing. The relation of the protective capacity of serum to that of milk was approximately 1/120 and 1/40 in the two animals. These figures do not differ much from those obtained by early investigators titrating the antitoxic content of serum and milk of animals undergoing immunization with diphtheria toxin. In the two experiments on calves, 2¼ and 18 days old, respectively, fed a highly protective serum, no increase in agglutinins or protective antibodies could be demonstrated. The postponement of colostrum to the twelfth and eighteenth hour, respectively, did not prevent normal growth.

AUTHOR'S SUMMARY.

THE IMMUNOLOGICAL SIGNIFICANCE OF COLOSTRUM. THEOBALD SMITH and RALPH B. LITTLE, J. Exper. Med. **51**:483, 1930.

Under certain safeguards, such as isolation, calves from a large dairy herd have been raised by feeding normal and immune cow serum in place of colostrum. The losses were about one of ten in the later experiments. This outcome may probably be improved by the subcutaneous injection of serum during the first day. This loss may be no greater than that under ordinary conditions, since sporadic deaths among calves are not infrequent. However, no satisfactory statistics are available for comparison with results as given.

AUTHORS' SUMMARY.

THE AMOUNT OF ULTRA-VIOLET RADIATION NECESSARY TO CURE RICKETS. G. H. MAUGHAN and J. A. DYE, Brit. J. Actinotherapy **4**:260 (March) 1930.

The rays having therapeutic value may not be the same for different diseases, but for rickets they lie in the ultraviolet near the line 2,968 Angström units. A certain percentage of these rays penetrate the epidermis and reach the blood capillaries in the dermis, from 0.2 to 0.5 mm. beneath the surface. In chickens exposure for one minute a day at a distance of 22 inches (55.8 cm.) would cause a cure of rickets in 95 per cent. When ten minutes' irradiation was given, only slightly better results were obtained than with the short exposure.

SANFORD, Chicago.

A STUDY OF THE ANTIRACHITIC VALUE OF IRRADIATED YEAST. STANISLAW K. KON and MIECZYSLAW MAYNZER, Lancet **1**:794 (April 12) 1930.

The authors report their experience at the Municipal Home for Foundlings, Warsaw, Poland. Pure fresh baker's yeast was air dried and then ground to an impalpable powder. Spread in a thin layer, it was activated by means of a quartz-mercury-vapor lamp for thirty minutes. The children to whom this yeast

was fed ranged in age from 4 months to 2½ years. Radiologically, advanced healing could be noticed in the course of a month, while the serum phosphorus increased markedly within ten days. The temporary stimulus to growth reported by Hess after the administration of autolysed or irradiated yeast to infants was not noticed by the authors.

LANGMANN, New York.

THE SIGNIFICANCE TO CLINICAL MEDICINE OF STUDIES IN CALCIUM AND PHOSPHORUS METABOLISM. DONALD HUNTER, Lancet 1:897 (April 26); 947 (May 3); 999 (May 10) 1930.

In his first lecture the author reviews briefly the normal mechanism of calcium and phosphorus metabolism. Man derives calcium principally from milk, cheese, butter, eggs, green vegetables and nuts. The daily calcium requirement of an adult is between 0.4 and 1 Gm., and until the growth of the skeleton is complete, the daily requirement exceeds this figure. Vitamin D seems to be the main factor governing the absorption of calcium, but whether or not it directly affects the utilization of calcium in the tissues remains for future experiments on metabolism to decide. Calcium is eliminated by the large intestine and to a less extent by the kidney. The normal figure for blood serum calcium (by the Clark and Collip modification of the Kramer-Tisdall method) varies between 9 and 11 mg. per hundred cubic centimeters, and in the cerebrospinal fluid between 5 and 6 mg. per hundred cubic centimeters.

The most obvious function of calcium in the body is the formation of bone. In the mammal, bone is the only considerable reservoir of calcium, and the skeleton can be drawn on not only for the skeletal needs of the fetus but also in the production of milk. Calcium also plays an important part in the blood and tissues by maintaining along with other ions a balanced system which determines the degree of irritability of muscle and nerve. It aids in the coagulation of shed blood.

Phosphorus is ingested in the food as nucleoprotein (meat), phosphoprotein (milk), lecithin (egg yolk, liver) and inorganic phosphate. The plasma and corpuscles contain equal amounts of inorganic phosphorus. The normal figures for inorganic phosphate in the blood (Briggs' method) vary between 2.5 and 3.5 mg. of phosphorus per hundred cubic centimeters; in children in whom ossification is more active, readings up to 5 mg. are found. The functions of phosphorus are: (1) It is essential to the storage or utilization of carbohydrate; (2) it enters into chemical changes which precede the contraction of muscle; (3) it is concerned with acid-base equilibrium, and (4) it is essential to the deposition of bone. Phosphateses are enzymes which hydrolyze phosphoric esters. They are widely distributed in mammalian tissues, chiefly in the epithelium of the intestinal mucosa in the kidney, in bone, etc.

Administration of parathyroid extract-Collip results in an increase of calcium output and also in an increase in the excretion of urinary phosphorus.

Parathyroid tetany is discussed, as well as cases of hyperparathyroidism, generalized osteitis fibrosa and exophthalmic goiter.

In the last lecture the author takes up conditions associated with defective absorption and utilization of calcium and phosphorus which give rise to diseases of bone.

Complete metabolism studies on human subjects show that there is an increase in calcium absorption when viosterol is administered.

Biochemistry has amply justified the view held for many years that rickets and osteomalacia are essentially identical. Osteomalacia is a deficiency disease endemic over wide areas in Northern India, Japan and Northern China and occurring sporadically in many other countries. Osteomalacia chemically resembles rickets caused by a low calcium content.

In hunger osteopathy, "styfsiekte" (a phosphorus deficiency disease of South African cattle), celiac rickets and renal rickets are briefly considered.

In rickets, osteomalacia and steatorrhea there is tetany (absorption and utilization are at fault), and the phosphorus content of the plasma is low as is the calcium content of the serum except in rickets, in which it is usually normal.

In hyperparathyroidism, postoperative tetany, hypoparathyroidism and renal rickets an inverse ratio holds between calcium and phosphorus. In hyperparathyroidism the calcium is high and the phosphorus low. In postoperative tetany and spontaneous hypoparathyroidism the reverse holds good. In renal rickets the plasma inorganic phosphorus is high and the serum calcium low.

In osteogenesis imperfecta no abnormality in the serum calcium, plasma phosphorus or calcium output has been satisfactorily demonstrated. The cause of the defective osteoblastic apposition is unknown.

LANGMANN, New York.

METABOLISM OF CARBOHYDRATES IN RICKETS. G. DE TONI, Arch. de méd. d. enf. **33**:129 (March) 1930.

The author presents this elaborate thesis, based on original studies in the Children's Clinic of the University of Bologna, as a contribution to the thirteenth congress of the Italian Pediatric Society, recently held in Turin. The knowledge of the pathogenesis of rickets has been enriched during the past decade by the study of avitaminosis, by the roentgenologic examination of rachitic bones and by the investigation of the effects of light, especially the ultraviolet rays, on rachitic processes. More recently, it has been augmented through the production of experimental rickets, the biochemical studies of the blood and tissues in this disorder and finally through the discovery of irradiated ergosterol. De Toni reviews these contributions at length and presents a comprehensive summary of the specific items of research which have clarified the views on aspects of rickets hitherto controversial. With this as a basis, the author develops his theories on the biochemical relations in rickets and particularly on the metabolism of the hydrocarbons, which up to this time has been indifferently considered.

De Toni's investigations led him to measure the lactic acid content of the cerebrospinal fluid instead of the blood. The objection to this may be made that as glycorachia is not comparable to glycemia, lacticorachia might differ from lactemia. In reply to this, the author recalls that research has already disclosed the fact that there is practically no difference in the lactic acid content of the blood and the cerebrospinal fluid. At least the difference is not comparable to the variation in the sugar and the chlorides. There appears to be a constant and perpetual equilibrium for lactic acid within and without the meningeal barrier. Six normal nurslings and sixteen infants with rickets were included in the series investigated by de Toni, the spinal fluid being removed during fasting and determinations made for lactic acid, sugar and inorganic phosphorus.

In another experiment, he attempted to confirm the conclusions reached by the aforementioned writers on alimentary glycemia in rachitic infants, using the same infants as in the first investigation. For the estimation of dextrose he employed the classic method of Folin and Wu; for the determination of phosphorus he followed the routine of Bell-Doisy-Briggs.

In the study of alimentary glycemia, de Toni gave an infusion of tea with 10 per cent dextrose, the total amount of the latter being 1.25 Gm. per kilogram of body weight. For two and a half hours thereafter the blood was examined every twenty minutes and compared with the picture made during the fasting stage. The results show that while there is almost no variation in the ratio of glycorachia in the well and the rachitic infant, lacticorachia and phosphorachia have remarkable differences. The average lactic acid index in healthy infants is 19 mg. per hundred cubic centimeters. The inorganic phosphorus in the cerebrospinal fluid averages 1.45 mg. per hundred cubic centimeters, while in cases of rickets it falls to 1.05 mg.

AMESSE, Denver.

MANAGEMENT OF HYPOTHREPSY IN NURSLINGS. N. J. SPYROPOULOS, Arch. de méd. d. enf. **33**:223 (April) 1930.

The author contributes, from the pediatric department of the University of Athens, a study of infantile athrepsy which he divides into three stages: (*a*) simple hypothrepsia of the first degree, (*b*) a moderately advanced or second degree stage and (*c*) hypothrepsia gravis or decomposition.

Each of these divisions has its special clinical features and its individual evolution and prognosis. The sources of this condition are invariably multiple, regardless of type; there is, practically always, undernourishment with digestive disturbances and, later on, infectious processes. Overfeeding or inappropriate diet in artificially fed infants are common initial factors, with tuberculosis ever ready to supervene. In many cases, hereditary syphilis furnishes the basis for the pitiful nutritional state; twin pregnancies, prematurity and congenital debility may influence the development of the infant. Spyropoulos stresses particularly the likelihood of malassimilation as a sequel to these defects, and the consequent failure to gain in weight, with functional disorders of various organs, especially of the liver and the ductless glands. It is this composite picture of disease in a subnormal infant which makes rational therapeusis difficult. The use of insulin, to combat glycolysis and to mobilize and utilize dextrose in the various tissues, seemed of considerable value and was employed in twelve cases in which specific infections could be excluded. These patients ranged in age from 8 months to 3 years; the formulas were carefully adapted to prevent overfeeding at the beginning of the treatment. Insulin was given in the usual way in doses of from four to six units twice a week. In two of the younger infants no benefit was shown, but in the remaining ten cases, considerable good resulted; the babies gained in weight regularly and their condition in general was greatly improved as shown by the prompt return of tissue turgor and a marked increase in hemoglobin; hypoglycemia was prevented by administering from 4 to 6 Gm. of dextrose before and after injection.

AMESSE, Denver.

GROWTH IN LENGTH AND WEIGHT IN TWINS: VII. THE KNOWLEDGE OF HEREDITY. H. Orel, Ztschr. f. Kinderh. **48**: 1, 1929.

Eight hundred and three pairs of twins on whom the author had previously reported were followed up and measured. The differences in body length and weight were less in the one-egg pairs of twins than in the two-egg pairs of like sex; this was true also of the differences in body weight. Of twenty-two pairs of one-egg twins in whom there was a difference in weight at birth, the difference persisted in twelve and disappeared in nine; in one pair the heavier twin was overtaken by the lighter. Of twenty-four pairs of two-egg twins of like sex, the difference persisted in fourteen and disappeared in none; in ten the heavier twin was overtaken by the lighter. When there was no difference in weight at birth, a difference appeared later in two of five pairs of one-egg twins. In pairs of twins of unlike sex, the girls were heavier in two cases and the boys in eleven cases; in three pairs of twins the babies were of the same weight. In seven cases the difference in length changed in favor of the boys. In two of three pairs of the same length, the boy progressed more slowly in development. In seven pairs the boy, and in nine pairs the girl, overtook the other twin in weight. In three pairs the boy, and in five pairs the girl, overtook the other twin in length. In one pair of one-egg twins there was a great difference in measurements at birth: one twin was 11 cm. shorter and 880 Gm. lighter than the other, was rachitic and anemic to a high degree, and was quite different in body form. The weaker baby lived, but the difference in measurements remained. When last examined, the girls are now almost 9 years old. One girl was 10 cm. shorter, but since the proportions were similar she looked like a miniature of the other.

How do these differences in weight come about? In two-egg twins a difference in weight can be caused genotypically; although the twin who was stronger at birth was not injured in intra-uterine life, the weaker twin overtakes him. Two-egg twins are like brother and sister, and real differences in weight frequently occur in them. They are an expression of different germ inheritances. In one-egg twins the difference in weight is caused phanotypically. One must assume that the bent in the germ to a definite body size is included in the chromosomes of the fertilized egg from which the twin develops. Both twins have within them genotypically the same size, which might be identical with that which the infant in a single birth might attain. One-egg twins without special differences in birth measurements as a rule show only small differences later. They usually do not develop more slowly than infants of single births. The lengths in Orel's cases, for example, show the same scattering in values as those of Camerer-Pirquet for infants of single births. The great differences of one-egg twins are caused not genotypically but phanotypically. Just when they occur is unknown, but there are three possibilities: 1. They could arise from unequal division of the fertilized egg cell or of the cell complex resulting from it; this would never happen with mathematical accuracy. 2. They could arise from intra-uterine development from the dynamic asymmetry due to the third circulation (anastomoses of the capillaries of the chorionic villi). 3. They could arise from extra-uterine undernourishment as a result of exogenous injuries. That the first possibility really leads to unequal development, Orel could not prove. It might lead, perhaps, to dynamic asymmetry. However that may be, the unequal development in utero is significant in this way; great differences at birth disappear or are reversed only in exceptional cases.

EMERSON, Boston.

RELATION BETWEEN WATER AND SODIUM CHLORIDE EXCHANGE IN A HEALTHY BABY. E. ROMINGER, I. BERGER and H. MEYER, Ztschr. f. Kinderh. **48**:43, 1929.

From studies on adults it is known that doses of sodium chloride are quickly excreted, and completely so with the exception of 6 or 7 per cent, which is not later detectible. It has been assumed that in the infant, sodium chloride cannot be stored and is immediately excreted, but the researches of these investigators show that the young baby regularly retains a considerable part (20 to 40 per cent) which is gradually and completely excreted after the administration of sodium chloride has been stopped. These observations stand in good agreement with the knowledge of the supermineralization of the bottle-fed baby.

EMERSON, Boston.

RESEARCHES ON THE DIGESTION OF CARBOHYDRATE IN BABIES: II. TESTS OF SUGAR TOLERANCE IN CHILDREN WITH NORMAL INTESTINES. H. PAFFRATH and H. SIERING-KAULLA, Ztschr. f. Kinderh. **48**:76, 1929.

On twenty-two babies with normal intestines, of the average age of 6 months, sugar tolerance tests were performed ninety-seven times. In research periods of two or three days the children received from 15 to 20 per cent solutions of Nährzucker (starch plus diastase), Kinderzucker (starch plus maltase), grape sugar, cane sugar and milk sugar. The cooking of solutions of Nährzucker and Kinderzucker did not influence their acceptability by the infants in comparison with solutions not cooked. Equally well borne were Nährzucker, Kinderzucker and grape sugar, although there was frequent vomiting during the Kinderzucker period; cane sugar and milk sugar were less well borne. Glycosuria seldom occurred and was not a characteristic reaction to any kind of sugar.

EMERSON, Boston.

RESEARCHES ON THE TYPE OF CARBOHYDRATE IN INFANTS: III. EXPERIENCES WITH KINDERZUCKER AND DISTURBANCES OF NUTRITION. H. PAFFRATH, Ztschr. f. Kinderh. **48**:86, 1929.

Kinderzucker introduced by Stöeltzner, two and one-half years ago, is similar to dextrin-maltose mixtures, purchasable at less cost and is to be looked on as practically pure grape sugar. In eighty-eight babies with disturbances of nutrition, Kinderzucker was replaced by Nährzucker. Of these patients twenty-three with acute dyspepsia were treated with rice water plus 10 per cent Kinderzucker and the slow addition of whole milk. A cure was obtained in two of three failures when the feeding was changed to rice water plus 10 per cent Nährzucker. The remaining sixty-five infants received with their milk mixtures alternately Kinderzucker and Nährzucker in 5 per cent supplements. The mild cases showed equal tolerance for both sugars. During the Kinderzucker periods, intertrigo occurred frequently. The Nährzucker was superior to the Kinderzucker in babies with unstable intestines. According to this experience, Kinderzucker stands between cane sugar and dextrin-maltose mixtures in its antidyspeptic activity.

EMERSON, Boston.

INJURY TO THE KIDNEYS OF A CHILD BY VIOSTEROL. WALTER PUTSCHAR, Ztschr. f. Kinderh. **48**:269, 1929.

Marked calcification of the tubules and interstitial tissue in the kidneys of an atrophic patient, a boy aged 5½ months, is described by Putschar. These injuries, after the exclusion of all other possibilities, are to be looked on, with the support of experimental research in the literature, as probably due to viosterol, which is obviously of less value for the nonrachitic children sick with some other disease, and may occasionally be dangerous. The calcifications occurred apparently in healthy tissue. Six drops of viosterol were given for ninety-six days; fifty days after the dosage was begun the urine was normal; twenty days later leukocytes, a trace of albumin and later crystals were found in abundance. There were no signs of rickets.

EMERSON, Boston.

Prenatal Conditions

FETAL BACTEREMIA: A CONTRIBUTION TO THE MECHANISM OF INTRA-UTERINE INFECTION AND TO THE PATHOGENESIS OF PLACENTITIS. ALFRED J. KOBAK, Am. J. Obst. & Gynec. **19**:299, 1930.

The occasional presence of streptococci and other organisms in the blood from the umbilical cord, sent to the laboratory for use in mediums, prompted an investigation on a large scale to determine in what manner the fetus becomes infected before or during labor. Thus 374 consecutive fetal blood cultures, aseptically drawn from the umbilical cord in the third stage of labor, were studied. Positive cultures were found in thirty-four cases, or about 9 per cent. In most instances these cases were associated with a prolonged rupture of the bag of waters. The organisms were found to be the type that usually frequents the vaginal canal in late pregnancies. Thus it is believed that they find their way into the amniotic fluid from which they get into the fetal circulation. The placentas were studied in all cases in which three cultures were positive, and also in any cases that had membranes unduly long ruptured and in which there was suspicion of utrapartum maternal infection. This study showed that the inflammatory reactions of the placenta is most often due to organisms in the amniotic waters. The organisms most likely break through the superficially placed chorionic blood vessels and enter the fetal circulation. In most instances this was only a transient bacteremia with no clinical significance. In a few instances of difficult birth, with a traumatism of the child from obstetrical procedures, severe and even fatal infection occurred. Four of the infants who died had the same bacteria in the heart blood as in the blood of the cord. Maternal infection also may take place in difficult labor.

KOBAK, Chicago.

THE PLACENTAL TRANSMISSION OF INSULIN FROM FETUS TO MOTHER. G. T. PACK and D. BARBER, Am. J. Physiol. **92**:271, 1930.

Anesthetized pregnant goats were subjected to laparotomy, and insulin was carefully injected into the palpated feti, care being taken to avoid loss in the peritoneal cavity. While the procedure was invariably followed by abortion, death of the feti being presumably due to hypoglycemic shock, such death did not occur during the period of the experiment, as was determined by palpation and abdominal auscultation. Determinations of blood sugar in the mother established the fact that there was transplacental transmission of the insulin.

EGGERS, Omaha.

SPONTANEOUS INOCULATION OF MELANOTIC SARCOMA FROM MOTHER TO FOETUS. F. PARKES WEBER, E. SCHWARZ and R. HELLENSCHMIED, Brit. M. J. **1**:537 (March 22) 1930.

A woman suffering from melanotic sarcoma was delivered three months before her death of a child who appeared at first to be healthy. When 8 months old, the child entered the hospital with an enlarged liver on which masses were palpated. These were later found to be melanotic tumors. With increasing cachexia, the child died two months later, minute nodules having developed beneath the skin shortly before death. The primary disease was apparently in the liver. At the time of birth, the placenta was infiltrated with masses of melanotic growth. The authors feel that the tumor cells must have passed from the mother through the placenta into the fetal blood stream. The blood in the umbilical vein having chiefly to circulate through the liver, some of the melanotic cells were caught up in the hepatic capillaries, and these cells were the parents of the melanotic tumors. This is probably the first report of a case of congenital malignant tumor due to intra-uterine inoculation of the fetus by the passage of malignant tumor cells from the placenta to the child by way of the umbilical vein. There have been many published examples and different varieties of inherited constitutional predisposition to malignant neoplasms, but the authors feel that their case is not of this sort.

RATTNER, Chicago.

ULCERATIVE DISEASE OF THE FETUS. L. OMBRÉDANNE and LACASSIE, Arch. de méd. d. enf. **33**:199 (April) 1930.

The prevailing idea that certain scars and mutilations found in the new-born are due to amniotic bands and adhesions exerting pressure on the fetus is attacked by these writers. Cases are reported with numerous illustrations in support of their contention that ulcerative processes, probably affecting the embryo before the forty-fifth day and due to causes as yet unknown, are responsible for the pitiful deformities found at intervals in every obstetric clinic. It is entirely improbable that these invasions are the result of bacterial or toxic action; the writers consider them to be rather the expression of a faulty circulatory equipment or a defective nervous system. While most of these unfortunates are born with cicatrices, there have been reported several instances (Kirmission, Ballantyne and others) in which the ulcerative lesions were unhealed. To these the authors add another case.

AMESSE, Denver.

TWO CASES OF CRANIOFACIAL DYSOSTOSIS OF CROUZON. P. PESME, Arch. d'opht. **46**:738 (Dec.) 1929.

Although tower skull has been known since the work of von Michel and Virchow, in 1912, Crouzon first described another type of malformation associated with optic atrophy. This condition is characterized by: (1) a cranial deformity somewhat resembling oxycephaly, (2) facial malformation, especially in regard to the nose and jaw with a resulting prognathism and (3) ocular disturbances

consisting of exophthalmia, divergent strabismus and loss of vision. Crouzon thought that a fourth characteristic was the hereditary and familial nature of the condition.

The author describes two cases, with excellent photographs and roentgenograms. In neither case was there evidence pointing to hereditary or familial traits. The pathology of this condition is complex. It is thought that premature closure of the bones of the skull best explains the condition. In oxycephaly it explains the intracranial hypertension. The involvement of the bones of the base account for the ocular manifestations. An atresia of the orbit results so that the eye itself rests in the orbit like an egg in an egg-cup. Compression of the nerve in its bony canal produces the atrophy. No definite etiology has been established. At the present time it is thought by Crouzon and Chatelain to be a hereditary dystrophy. The condition is of interest to ophthalmologists because of the involvement of the optic nerve and the eye.

MARLOW, Syracuse, N. Y.

CONGENITAL STENOSIS OF POSTERIOR URETHRA. M. BECK, Beitr. z. path. Anat. u. z. allg. Path. **83**:13, 1929.

Beck reports two cases of congenital infracollicular stenosis of the urethra. In one case in a boy aged 3½, the stenosis was situated at the junction of the prostatic and membranous urethra. The corpus spongiosum of the penis, with the urethra, lay dorsal to the corpora cavernosa, which were not separated from each other by the usual median longitudinal septum. The meatus of the glans penis was dorsal, the coronary sulcus ventral. The bladder was small and contracted. The ureters were greatly dilated and convoluted. The wall of the lower segment of the left ureter contained a rudimentary accessory ureter. The renal pelves were dilated. In the second case, in a new-born male infant, the stenosis was situated in the membranous portion of the urethra. There were no anomalies of the penis except phimosis. The left testis was retained in the inguinal canal, the right in the abdomen. The bladder was distended and reached to the level of the umbilicus. The ureters were tortuous and moderately dilated. An accessory ureter situated in the anterior and mesial wall of the main ureter of each side opened into the bladder laterally to the normal ureteral opening. The accessory ureters ended blindly above. The renal pelves were dilated. The kidneys were small and polycystic. The pelvis of the left kidney was situated anterior to the lower pole of the kidney.

SCHULTZ, Chicago.

MULTIPLE MALFORMATIONS IN A HYPOPLASTIC PERSON. VOJIN LAZAREVIĆ, Virchows Arch. f. path. Anat. **273**:445, 1929.

An idiotic girl, aged 13 years, had a family history that was irrelevant. There were five other healthy children. At the age of 3 paralysis of the left arm and leg developed. She often choked while eating; palpitations were always present; menstruation had not begun. The clinical diagnosis was: spastic infantile hemiplegia, mitral insufficiency and stenosis, defect of septum. Death occurred from cerebral embolism. The anatomic diagnosis was: primary microgyria of the right cerebral hemisphere; defect in the septum of the ventricles and auricles, congenital insufficiency of the venous ostia; thymus persistens; hypoplasia of the arteries; hyperplasia of the lymphatic apparatus; extensive polyposis adenomatosa of the large intestine; abnormal lobulation of the right lung, liver, spleen and kidneys; large ovaries with follicular cysts; pigmented nevi of the skin.

PLAUT, New York.

FOUR CASES OF CONGENITAL OCCLUSION OF INTESTINE. HANS NAHRATH, Virchows Arch. f. path. Anat. **273**:747, 1929.

The fact that between multiple stenoses of small intestine, meconium and lanugo could be found, leads to the conclusion that in this one instance the cause of the occlusion must have come from within the intestine. The outer layers and

mesenteric vessels were found completely intact, without any angulation or torsion. The time when the liver begins to secrete bile is much later than the time when parts of the intestine pass through a solid stage. Thus, fetal enteritis is given as a cause for this case of congenital multiple stenoses of small intestine. In the three other cases described, disorders in the obliteration and separation of the omphalomesenteric duct had been leading to meconium peritonitis.

PLAUT, New York.

CONSTITUTIONAL ANOMALIES OF THE THORAX AND DIAPHRAGM. KARL HITZENBERGER, Wien. klin. Wchnschr. **43**:367 (March 20) 1930.

The author gives a résumé of constitutional anomalies of the thorax and diaphragm.

In discussing anomalies of the thorax, he points out that they may be either a part of a total constitutional anomaly or a partial anomaly of the chest alone. In the infantile type of chest, which is apt to lead to emphysema in the adult, the etiology is due not only to the conformation of the chest but also to recurrent bronchitis. The asthenic type of chest is also a well known habitus. This type is often said to be associated with tuberculosis due to the poor movement of the upper part of the thorax. However, the well known primary infection is usually found not in the apex but in the lower lying parts of the lung, and probably the old accepted idea that the asthenic type of thorax predisposes to tuberculosis is not true.

The author describes cervical rib which may cause pressure on nerves and great vessels. He also discusses anomalies of the sternum, such as pigeon breast and funnel breast.

In discussing constitutional anomalies of the diaphragm he points out the abnormally high and the abnormally low positions of the diaphragm. The latter position accompanies the asthenic type of thorax. The costophrenic angle is more obtuse than normal, and the diaphragm appears to lie horizontally. The excursions of the diaphragm are smaller than normal, and with quiet breathing one sees a minimal, often hardly visible, movement. The inspiratory reserve is smaller than the expiratory.

In the abnormally high standing diaphragm one must consider traction from above by the lung or pressure from below through enlargement of abdominal organs.

A. F. ABT, Chicago.

THE HEREDITARY TRANSMISSION OF ACQUIRED IMMUNITY THROUGH THE GERM PLASM. OTTO HERRMANN, Zentralbl. f. Bakteriol. (Abt. 1) **113**:460, 1929.

The author finds that the acquired immunity in rabbits to rabies virus is transmitted to the young and may persist for six to eight months.' This immunity has been transmitted by females even when the pregnancy began from six to nine months after the termination of the immunization. The immunity has also been transmitted by the males as long as from one to seven and one-half months after the termination of the immunization. When both parents are immune a greater proportion of the young are immune. Apparently the immunity may even be transmitted to the third generation, although more animals must be studied to confirm this point.

CANNON, Chicago.

Acute Infections

SOME FACTORS IN THE DIPHTHERIA PROBLEM. CHARLES HERRMAN, Arch. Pediat. **46**:627 (Oct.) 1929.

Among the problems discussed are the following: (1) immunity and the Schick test in the new-born infant; (2) the Schick test in older children; (3) the effect on the test of differences in the degree of congestion; (4) family predisposition

and hereditary factors; (5) periodicity, and (6) what has been accomplished by toxin-antitoxin immunization in New York.

Immunity to diphtheria in the new-born and young infants is largely due to the presence of antitoxin in the blood, but a negative reaction to the Schick test is partly due to a lack of reactivity of the skin. In a majority of cases the Schick test is an accurate index of immunity. It is an index of the amount of exposure to infection, but not an absolute index of the ability to develop antitoxin.

Antitoxin may develop spontaneously as a result of "serologic maturity." The ability to develop antitoxin is largely dependent on hereditary factors. Where active immunization is not employed, epidemics occur periodically. Active immunization with toxin-antitoxin has proved successful. A certificate of successful immunization should be required for admission to kindergarten and school.

WILSON, Norfolk, Va.

THE CAUSES FOR SEVERITY IN ONE HUNDRED CASES OF SEVERE DIPHTHERIA. EDWARD B. SHAW and H. E. THELANDER, Arch. Pediat. **47**:178 (March) 1930.

In a series of 100 cases of severe and highly fatal diphtheria the reason for severity was unusual virulence in only 6. In 92 cases, delayed diagnosis was to blame. In 41 cases, the responsibility for delay rested with the parents, and in 51 with the physician. In the majority of these patients under a physician's care from the first, fairly simple diagnostic measures, such as early and repeated cultures, and frequent careful examination might have speeded the diagnosis greatly. In 12 cases, complicating disease was overlooked because too much attention was paid to the primary illness and not enough to the possibility of intercurrent infection until diphtheria was far advanced.

WADDELL, University, Pa.

REVIEW AND OBSERVATION ON ONE CASE OF HYDROPHOBIA. C. C. WEBB, J. Florida M. A. **16**:401 (March) 1930.

The author describes the stages of hydrophobia. The first or premonitory stage began two months after a patient was bitten by a rabid dog. The symptoms were pain and irritation about the bite, depression, headache, fever, photophobia and dysphagia. The second stage soon followed, with excitement, restlessness, hyperesthesia, laryngospasm, and maniacal symptoms alternating with quiet intervals. The paralytic stage came on two days later; death occurred by syncope.

BIEKER, St. Petersburg, Fla.

DIPHTHERIA PREVENTION IN NIAGARA FALLS. EDWARD E. GILLICK, New York State J. Med. **29**:1441 (Dec. 1) 1929.

Of 21,000 children less than 14 years of age in Niagara Falls but 8,752 had been immunized against diphtheria at the end of 1927. Only 2 per cent of the preschool children had been protected. By a vigorous campaign 6,550 more were immunized, and the percentage of immune preschool children was raised from 2 to 48.5. There has been a marked fall in the incidence of the disease.

AIKMAN, Rochester, N. Y.

THE NATURE OF THE LESIONS IN GENERALIZED VACCINIA IN RABBITS. JAMES MCINTOSH and R. W. SCARFF, J. Path. & Bact. **32**:551, 1929.

With certain strains of virus, generalized vaccinia in rabbits regularly occurs, both after scarification and after intravenous inoculation. All the lesions of generalized vaccinia show the histologic picture of an infective granuloma affecting primarily the smaller blood vessels with endothelial proliferation, necrosis of tissues and subsequent fibrosis. The visceral lesions are due to the direct action of the vaccinia virus and not to the activation of a latent infection.

AUTHORS' SUMMARY.

LARYNGEAL AND PULMONARY COMPLICATIONS IN INFLUENZA. M. LESNE, C. LAUNAY AND WAITZ, Bull. Soc. de pédiat. de Paris **27**:249 (May 21) 1929.

There were thirteen patients with pleuropulmonary inflammation who had pleural effusion. The fluid was sterile in all instances. One of the thirteen patients died. Fourteen patients developed edema of the larynx, and of this number four died. Bacteriologic examination of the laryngeal exudate removed at laryngoscopic examination showed staphylococci, streptococci and pneumococci but no diptheria bacilli. In many of the roentgenograms taken pathologic changes of the hilus were found especially in children from 2 to 4 years of age; the change was mostly grandular, with some extension into the parenchyma of the lungs. The children showed a few or no physical signs. The tracheobronchial glands seem to be an intermediary station between infections of the upper respiratory tract and those of the pulmonary parenchyma. The roentgenologic increase in the hilus shadow may perist for a long time in these cases, and from this point of view, these "la grippe" infections resemble pertussis and measles.

BENJAMIN, Montreal, Canada.

ANGINAS WITH DIPHTHERIA BACILLI AND DIPHTHERITIC ANGINAS OF BENIGN COURSE IN CHILDREN IMMUNIZED WITH ANATOXIN. B. WEILL-HALLÉ, GOROSTIDI, DELTHIE and PAPAYANNOU, Bull. Soc. de. pédiat de Paris **27**: 431 (Oct.) 1929.

Ten cases are cited of children with diphtheria who had previously received anatoxin immunization. Three cases may be discounted—one patient had ordinary angina and was probably a diphtheria carrier; the other two cases were doubtful clinically, and the diphtheria bacilli disappeared from the throats after antitoxin was given. Seven of the ten patients who had positive throat cultures had obvious clinical diphtheria; they were all given antitoxin, and the throats were all free from diphtheria bacilli after from fifteen to eighteen days. Three of the cases appeared from eight to eleven days before the onset of measles; whether the period of incubation rendered them more susceptible to diptheria, if it did not lessen their antidiphtheritic immunity, is a question that suggests itself. Diphtheria undoubtedly occurs in a small number of children who have previously been given three injections of anatoxin, possibly 3 per cent, and this dose does not detract from the usefulness of immunization against diphtheria with anatoxin, which renders the vast majority of children permanently immune. To explain the cases which form the basis of the paper, the authors mention these possibilities; idiosyncrasy, unusually slow development of immunity, counteracting influence of an intercurrent infection, some change having taken place in the anatoxin used. They recommend that a Schick test be performed on all children, especially those in institutions, one month after the third injection of anatoxin, and that all those who give positive reactions be given a fourth dose of anatoxin. They emphasize strongly the importance of administering antitoxin to any child who shows evidence of diphtheria even though the child may previously have had three injections of anatoxin.

In the discussion, Coffin relates the case of a girl, aged 6 years, who was given three injections of 0.5, 1 and 1.5 cc., respectively, at intervals of fifteen days between injections. A severe case of diphtheria developed exactly thirty days following the last injection of anatoxin; later the patient had paralysis of the soft palate, larynx, neck and limbs. In her sister, aged 2 years, who had received exactly the same dosage of anatoxin on the same days as the older girl, mild diphtheria also developed on the thirtieth day after the last injection of anatoxin; in her case the disease subsided rapidly after she had been given 20 cc. of Roux serum.

BENJAMIN, Montreal, Canada.

DIPHTHERIA OF THE NEW-BORN INFANT AND OF THE NURSLING. A. B. MARFAN, Rev. franç. de pédiat. **6**:1 (Jan.) 1930.

In this study, Marfan has brought out observations of considerable importance for the care of the infant. Many cases of coryza, conjunctivitis and otitis, apparently of the common type, have been found to be due to inflection with the Klebs-Löffler bacillus. Left alone, these may go on to bronchopneumonia, often fatal, in which the diphtheria bacillus may be recovered from the lungs. Infections of the umbilicus and eczematous skin lesions, particularly retro-auricular, are sometimes due to the diphtheria bacillus.

LESLIE, Evanston, Ill.

POSTVACCINAL ENCEPHALITIS. E. GILDEMEISTER, Centralbl. f. Bakteriol. **110**: 120, 1929.

This paper is a general discussion of the problem of postvaccinal encephalitis. The cases occurring particularly in Europe and England are reviewed and discussed. The view most stressed is that of the so-called activation theory; namely, that the vaccination activates an invisible virus already present in the body of the person vaccinated. No definite facts, however, are given to explain the phenomenon.

CANNON, Chicago.

ANTITOXIN IN THE BLOOD OF NATIVES IN EAST AFRICA. F. KLEINE and H. KROÓ, Deutsche med. Wchnschr. **56**:46 (Jan. 10) 1930.

While on a journey in East Africa, one of the essayists applied Schick tests to 101 natives (95 children and 6 adults). The toxin used was an especially prepared product; the unused portion was sent back to laboratories in Germany for checking. All of the negatives gave negative reactions. Examinations were made of the serum of eleven patients. All of these showed a high titer of antitoxin according to the technic of Roemer. Furthermore, the scarlet fever antitoxin content of the serum was high. In view of the fact that these diseases are uncommon in the region, the results are surprising. The authors offer several explanations of this discovery and suggest that the subject is worthy of further investigation.

SCHERER, Duluth, Minn.

FURTHER EXPERIENCES WITH DIPHTHERIA IMMUNIZATION. W. POCKELS, Deutsche med. Wchnschr. **56**:48 (Jan. 10) 1930.

The writer refers to the work with diphtheria immunization done in Berlin and previously abstracted in the *Deutsche medizinische Wochenschrift*. He calls attention to the danger of later serum diseases in the uses of antitoxic serum neutralization of the toxin. Experimentally he determines the antitoxin titer produced by the various preparations examined and decides that these must be greatly enhanced if successful results are to be obtained. He suggests that the use of underneutralized preparations, while they may produce some untoward symptoms, is at present the most satisfactory.

SCHERER, Duluth, Minn.

COMPLICATIONS IN THE COURSE OF VACCINATION. E. MEDER, Deutsche med. Wchnschr. **56**:99 (Jan. 17) 1930.

The author reports two cases of vaccination in which the course was not typical. In the first case the pustules were infected with a typical impetigo; they healed without scarring. In the second case there was a definite recurrence at the edge of a pustule thirty-seven days after vaccination; healing was uneventful.

SCHERER, Duluth, Minn.

POSTVACCINAL ENCEPHALITIS. E. PASCHEN, Deutsche med. Wchnschr. **56**:219 (Feb. 7) 1930.

The author discusses the various vaccines on the European market. Some of these are brought out and advertised as being produced without the usual rabbit inoculation, and hence are supposed to be free from the encephalitis-producing factor. He shows, however, that passage through rabbits has nothing to do with the incidence of encephalitis. He further discusses numerous other hypotheses, only to discount all of them. As the one bright spot in all the reports of postvaccinal encephalitis, he cites the work of Horder and Heckman who have shown that the early use of immune serum has a beneficial influence on the disease.

SCHERER, Duluth, Minn.

THE CLASSIFICATION OF CLINICAL SCARLET FEVER IN CHILDREN. A. A. KOLTYPIN, Jahrb. f. Kinderh. **122**:302 (Jan.) 1929.

Koltypin attempts a clinical classification of scarlet fever into mild and severe types, according to the manifestations of intoxication, disease of the autonomic nervous system and the condition of the pharynx. For therapeutic reasons an exact classification according to clinical symptoms is necessary, because antitoxic serums are administered only in severe, primary toxic cases. In mild cases intoxication and necrotic angina are absent.

In the average case there is necrotic angina with definite intoxication but no early vegetative disturbances. In the first week, however, there is increased tonus of the sympathetic nervous system (increased blood pressure, tachycardia, heart not dilated, white dermographism, negative or paradoxic Aschner phenomenon, perspiration absent, slight salivation, dry skin). In the second week, on the contrary, the sympathetic tonus is lowered, and the paresympathetic system predominates (low blood pressure, slow and arrhythmic pulse, enlarged heart, white dermographism, positive Aschner phenomenon, salivation). In later stages the tonus of the sympathetic system becomes equalized.

In severe cases of scarlatina there is a diminished "sympathico-adrenal" tonus and usually severe symptoms. In this primary toxic scarlet fever, as in diphtheria, damage to the nervous tissue may be observed histologically. In the severe septic form there are deep necrosis of the pharynx, early marked lymphadenitis and septic complications.

A. F. ABT, Chicago.

SCARLATINAL NEPHRITIS. B. S. HIRSCHBERG and M. E. SSUCHAREWA, Jahrb. f. Kinderh. **122**:340 (Jan.) 1929.

Hirschberg and Ssucharewa have drawn the following conclusions from extensive material:

1. Nephritis may occur at any time during the course of scarlet fever (11.9 per cent of all cases of nephritis begin during the first week).

2. The occurrence of early cases is difficult to bring into harmony with the allergic theory of scarlatinal manifestations.

3. Early symptoms are: increased blood pressure, an enlarged heart, accentuation of the second pulmonic beat and increase in weight. In early cases it is important to note these cardiovascular symptoms.

A. F. ABT, Chicago.

VACCINATION AND THE NERVOUS SYSTEM. A. MADER, Jahrb. f. Kinderh. **123**: 11 (March) 1929.

Mader reviews the previous literature on vaccination and the nervous system, and presents six of his own cases of encephalitis, in which there was complete recovery. There were noteworthy differences in the period of incubation. In four first vaccinations it was from seven to twelve days; in an eleven year old revaccination it was four days, and in an infant aged 6 months it was seventeen

days. In most of the cases there was an agreement of the neurologic symptoms (a positive Babinski reflex and absence of ocular muscle palsy), and in several the encephalitis was associated with meningitic or myelitic symptoms. Postvaccinal encephalitis may present the most varied clinical and anatomic manifestations and may affect any part of the central nervous system. The six reported cases occurred at a time when there was no question of epidemic encephalitis.

The following facts are suggested in the prophylaxis of postvaccinal encephalitis. If possible, vaccinate in the first six months of life. Febrile convulsions or spasmophilic manifestations may be induced, however. Late vaccinations are the most dangerous.

Nervous children or those with neurologic diseases should be excluded. In times when encephalitis, poliomyelitis or meningococcus meningitis are epidemic, vaccination should be postponed. It is sufficient to make one to two superficial scarifications with as little lymph as possible. It is still undecided whether the intracutaneous method of vaccination with diluted lymph prevents these complications. The morbidity is very small. Gins presents figures for Germany; a single complication in 700,000 vaccinations.

A. F. Abt, Chicago.

Typhus in Children (600 Cases). A. A. Koltypin, Jahrb. f. Kinderh. **123**: 27 (Feb.) 1929.

According to Koltypin, typhus is not a genuine disease of childhood, older children being affected more frequently because of their more intimate contact with affected adults.

Because of the necessary intermediate host, pediculosis vestimenti, the morbidity is slight in early childhood. The course in children as well as in adults is mild. Complications are rare and mild; mortality is slight. In infants there are often very mild, atypical forms, which are frequently unrecognized. In the differential diagnosis one must consider smallpox, measles, typhoid and relapsing fever. Prophylaxis is thoroughly discussed. The care of these patients presents no particular difficulties. The appetite remains unaffected. There is no specific treatment. The injection of serum from convalescent patients has no influence on the course of the ailment.

A. F. Abt, Chicago.

Atypical Coli and Milk Infection. Georg Abraham, Jahrb. f. Kinderh. **123**:80 (Feb.) 1929.

Abraham reports that in a period of three weeks twenty-three children, who previously were healthy became suddenly ill with severe and frequent vomiting. The stools remained normal, there was no fever, and the urine was free from albumin and sugar. The patients looked toxic. After a tea diet for two days there was complete relief from symptoms. The source of infection was the milk; it had been boiled three times, but the bottles into which it was poured had not been sterilized.

In the vomitus, in the aspirated gastric contents and in the stool of affected children the same types of *Bacillus coli* were demonstrated as were found in the raw and boiled half milk and whole milk that had been given. In the buttermilk there were no pathogens, and none of the children nourished on buttermilk vomited.

The bacillus that was isolated was tested with the various sugars and alcohols according to Adam and was identified as a unified group, distinct from the dyspepsia and pyuria type of *B. coli*.

A. F. Abt, Chicago.

Immunization Against Measles. H. Knauer, Jahrb. f. Kinderh. **123**:296 (April) 1929.

The injection of from 15 to 30 cc. of adult blood does not always serve effectively in the prevention of measles and the complicating pneumonias. Knauer reports observations which indicate that the serum of people who are constantly

in contact with patients with measles affords better protection than the usual adult serum (increased titer because of active immunization). Absolute immunity is not desirable, the author thinks, because a mild course does not endanger the child and on the other hand the mild infection may induce a lifelong immunity.

A. F. Abt, Chicago.

Nephrosis and Tetany. K. Klinké, Jahrb. f. Kinderh. **129**:300 (April) 1929.

In a boy, aged 6 years, who had typical lipoid nephrosis there occurred increased excretion of water of unexplained origin, followed by tetany (painful carpopedal spasm, cathodal opening contraction, 0.3 ma.) Klinké did not see any relationship between this case and a case of benign erysipelas in which the patient had been treated a few days previously by an injection of scarlatinal serum. In spite of the acidosis (as demonstrated by the p_H of the urine and diminished carbon dioxide capacity of the blood), tetanic manifestations may arise in nephrosis, particularly when there is increased calcium retention and a marked absorption of the complex calcium compounds by the serum albumin of the blood.

A. F. Abt, Chicago.

Results with the Hippocratic Biers' Method of Cauterization in Childhood. S. Wolff, Jahrb. f. Kinderh. **128**:328 (April) 1929.

In three cases that had failed to respond to the usual modes of therapy, S. Wolff utilized Biers' method of cauterization. In two instances this was a life-saving measure (staphylococcus endocarditis gravis after scarlet fever and severe endocarditis after scarlet fever). In a third child who had been running a fever of unknown causation for months after an attack of scarlet fever, there was a prompt cessation of the fever three days after the cauterization (*Med. Klin.* **24**:496, 1928).

A. F. Abt, Chicago.

Chronic Infections

Treatment of Interstitial Keratitis with Special Reference to the Use of Bismuth. Carroll S. Wright and H. H. Perlman, Am. J. Syph. **14**:169 (April) 1930.

The authors' conclusions are: "From our studies, we believe that the best treatment for interstitial keratitis consists in the conjoint use of sulpharsphenamine and bismuth or the intravenous use of neoarsphenamine followed by intramuscular injection of bismuth alternately or else immediately following a course of one by a course of the other. We believe that bismuth, by all means, is an important weapon in the therapeutic armamentarium against congenital syphilis."

Royster, University, Va.

Pulmonary Syphilis. Alvis E. Greer, Am. J. Syph. **14**:195 (April) 1930.

The author quotes from Karshner the following classified criteria of pulmonary syphilis: "(1) the pneumonic form, (2) the gummatous processes, (3) syphilitic pulmonary sclerosis, (4) bronchiectasis and (5) suppurative processes, ulcerations and gangrene."

A case is reported which conforms to these criteria.

Royster, University, Va.

Syphilis and Pregnancy. Chris R. Halloran, Am. J. Syph. **14**:222 (April) 1930.

"Although pregnancy does not apparently decrease susceptibility to infection with *Treponema pallidum*, the defense mechanism of pregnancy alters the clinical

manifestations of syphilis in such a way that primary and secondary lesions are frequently either absent or very mild: Although the Wassermann reaction in pregnancy cannot be relied upon, with the same degree of assurance as in the nonpregnant, a strongly positive blood Wassermann verified on repetition is diagnostic of syphilis. The blood Wassermann of the infant of the syphilitic woman is not reliable for the first month of life. The serologically and clinically normal child of a syphilitic mother must be kept under close observation and placed upon antisyphilitic treatment immediately should definite evidence of the disease become manifest. The pregnant woman tolerates a modified form of antisyphilitic treatment well, though the same unusual results are occasionally encountered as in treatment of the nonpregnant. A report of a nitritoid reaction in the seventh month of pregnancy is given."

ROYSTER, University, Va.

SPECIFICITY OF LIGHT ACTION IN TUBERCULOSIS. WINTHROP M. PHELPS, J. Bone & Joint Surg. **12**:253 (April) 1930.

The component parts of natural sunlight differ greatly, not only in different localities, but even from hour to hour in the same locality; hence, if natural sunlight is to be used in the treatment for disease, it is necessary to measure the actual amount of radiation given. The apparatus used by the author is described. Various filters were used to screen out undesirable rays of the sun's spectrum, and carbon arc lights with a known spectrum were also used. The results obtained are shown in tabulated form.

The author's conclusions can be summed up as follows: 1. Heliotherapy in tuberculosis can be carried out as effectively at sea level as elsewhere. 2. Longer exposures can be given if the erythema and tan-producing rays (from 300 to 320 millimicrons) are absent or of small quantity. 3. Wave lengths between 320 and 380 millimicrons were shown to be active, and this band is present in carbon arcs of 25 amperes or more, using carbons of known spectral distribution. 4. Sinuses were not directly exposed to the light and the results were excellent.

RYAN, Vancouver, B. C.

CARBON ARC LIGHT TREATMENT IN BONE AND JOINT TUBERCULOSIS. KATHARINE PARDEE, J. Bone & Joint Surg. **12**:270 (April) 1930.

A Schwartz high intensity carbon arc light was used in the treatment of twenty-two children during the winter months.

Judging by the change in the blood cells, weight and general appearance, there was a definite improvement in sixteen, slight improvement in three, no change in two, and one child was apparently made worse. The lower the hemoglobin reading at the start of the treatments, the greater the increase under treatment. This same statement applied to the number of red cells in the blood. During the winter months the average child tends to lose weight, whereas in the group studied there was an average gain of nine-tenths pound (408 Gm.). The children were more animated, made more noise and ate better.

Roentgenograms were taken in all of the children in the group, as well as in seven children in a control group. All of the children showed improvement in the roentgen observations whether in the exposed group or the control group, especially in the production of fusion in joints, but the results in the untreated group did not approximate the results in 85 per cent of the exposed children.

Thirty-three per cent of the children showed a rapid initial rise in blood counts followed by a fall. It is suggested that the continuous treatment may have been more than the children could well tolerate and that lesser dosages of light might produce better results. Blonds do not respond as well as brunettes.

Sinuses that were not directly exposed to the light healed, whereas those which were directly exposed did not, although there was marked improvement in the condition of the surrounding skin.

RYAN, Vancouver, B. C.

DELAYED OSSIFICATION IN CONGENITAL SYPHILIS. G. J. LANDA and V. P. PANOW, Ann. de dermat. et syph. **1**:403 (April) 1930.

The authors compared the evolution of ossification of the wrist (by roentgenograms) with that of normal wrists. In syphilis they found a definite retardation of ossification in about 60 per cent of the cases. Their results show the definite dystrophic influence of the disease on ossification, even in infants without clinical or serologic signs of syphilis, but born of syphilitic parents. Since retarded ossification occurs in other diseases, it cannot be considered as a certain diagnostic sign of syphilis; but in the more marked instances of delayed ossification it is an indication of decided significance.

MICHAEL, Houston, Texas.

RECENT OBSERVATIONS ON INFANTS GIVEN B.C.G. DURING THE FIRST TEN DAYS OF LIFE. NOBÉCOURT and KAPLAN, Bull. Soc. de pédiat. de Paris **27**:204 (May 21) 1929.

Infants from 1 to 10 months of age, who had been given B.C.G. before they were 10 days old, showed about the same number of positive as negative skin reactions to tuberculin. Those negative to the Pirquet tests showed no signs of any localized tuberculosis; three fourths of those positive to the Pirquet tests showed some signs that were suggestive of tuberculosis. During life, it is impossible to determine whether the B.C.G. or the Koch bacillus is responsible for the clinical picture, since either one or the other may produce a positive Pirquet reaction. In one case a guinea-pig inoculated with pus from an infant with osseous tuberculosis showed definite evidence of tuberculosis. In three autopsies, there was no macroscopic evidence of tuberculous lesions in two of the infants, and the third showed a caseous mesenteric lymph node, which did not produce tuberculosis in the guinea-pig. Most of the infants, whether their Pirquet tests were positive or negative, had not been exposed to persons known to have tuberculosis. It is difficult from clinical evidence alone to pass judgment on B.C.G., as to both its harmfulness and its immunizing action.

BENJAMIN, Montreal, Canada.

REPORT ON TWENTY-THREE INFANTS IMMUNIZED WITH B.C.G. G. KRIKORK, Bull. Soc. de pédiat. de Paris **27**:270 (May 21) 1929.

The author reports that none of twenty-three infants who had been given B.C.G. immediately after birth from four and a half to one year previously had died. They all lived in families in which one or more persons were known to have open tuberculosis. All of the children were in good health. The immunization did not exclude the possibility of infection with virulent tubercle bacilli, but the immunized children seemed to have acquired defensive powers which gained them the upper hand in the fight between these bacilli and the hosts in many cases in which the bacilli seemed the more probable to win out.

BENJAMIN, Montreal, Canada.

CONGENITAL SYPHILIS AND THE WASSERMANN REACTION. L. QUEYRAT, Bull. Soc. franç. de dermat. et syph. **37**:378 (March) 1930.

Queyrat calls attention to the frequent Wassermann negativity in infants with occult congenital syphilis. The medical profession as a whole needs instruction on this point, as many physicians do not know that in infantile congenital syphilis the Wassermann test is frequently negative. Parents, who get most of their medical information from their family physician, are likely to be deluded into a false security by the Wassermann report. A case in point was detailed.

MICHAEL, Houston, Texas.

BONE DISTURBANCE IN CONGENITAL SYPHILIS OF INFANCY: OSTEOCHONDRITIS. M. PÉHU and A. POLICARD, Rev. franç. de pediat. **5**:655 (Dec.) 1929.

An excellent presentation of the histologic pathology of osteochondritis is given. The authors contrast the changes in rickets with those in syphilis, showing that in the former the changes are in the cartilaginous zone and the line of calcification, whereas in the latter the change is in the area of resorption, there being more than normal resorption with the production of a thinned out bone. The authors feel that the cause of this increased resorption is an over-vascularization which is readily demonstrated histologically. Since these changes are always symmetrical, it is suggested that they are due not to a local action of the spirochete, but to a general effect of the disease on the vasodilators of the nervous system. Further differentiation from the normal consists in the presence of connective tissue in that part of the bone ordinarily occupied by hematopoietic tissue.

LESLIE, Evanston, Ill.

HEREDITARY SYPHILIS IN OTONEURO-OPHTHALMOLOGY. G. WEILL, Rev. d'oto-neuro-opht. **7**:670 (Nov.) 1929.

It is rare to find ocular manifestations of syphilis in the new-born, although syphilitic coryza is regularly found at this period. The ocular lesions develop later under two forms: 1. Chorioretinitis, which is discovered only by the ophthalmoscope; owing to the difficulty of the examination, it is often undiscovered until much later. It is an important sign and permits a diagnosis of hereditary syphilis in otherwise doubtful cases. The period of its manifestation extends from the first few months to the age of 4 or 5 years. 2. Late congenital syphilis occurs in the period extending from the age of 5 or 6 years to beyond puberty, ocular manifestations occurring even at 30 years of age or more. It is characterized by interstitial or parenchymatous keratitis, and is of great interest to neurologists and otorhinologists as well as to internists. This condition is often accompanied by gummatous osteitis of the nasal septum, labyrinthine deafness and dacriocystitis.

The great interest attaching to interstitial keratitis and chorioretinitis is that both leave sequelae which persist during the life of the patient, the former as deep vascularization of the cornea, the latter as peripheral pigmentary deposits in the retina.

On account of its interest in the three specialties as well as in general medicine, attention is called to syphilis in the third generation. Some authorities believe in a true transmission of syphilis to the offspring of persons with hereditary syphilis, while others maintain that the syphilitic infection merely prepares the ground for all sorts of diatheses, dyscrasias, cachectic states and endocrine disturbances. Attempts have been made to decide this question by researches, especially by oculists, on the ultimate fate of children of persons with proved cases of hereditary syphilis. Treacher Collins found, among twelve mothers afflicted with parenchymatous keratitis, that there were sixty living children and five miscarriages. Twenty-six of the children died in the first year of life; twenty-five of the remainder were well, and nine had various distrophies. Igersheimer reported on fifty-seven children of parents with interstitial keratitis, of whom ten died at an early age, one was stillborn and there were eight miscarriages. Among twelve of the children, the Bordet-Wassermann reaction was positive only in one. Sidler Huguenin examined sixty-five children of parents with interstitial keratitis by roentgenograms of the epiphyses of the knee joint, and made Wassermann tests. The latter was found positive only once, and the films were all negative.

The author's investigations of a small number of patients revealed no manifest signs of syphilis but they were, in general, thin and sickly. His conclusion is that persons with hereditary syphilis produce children in whom the Wassermann reaction is negative but who present various pathologic changes of the endocrine system.

DENNIS, Colorado Springs, Colo.

EARLY DIAGNOSIS OF TUBERCULOSIS BY THE VERNES REACTION: ITS DIAGNOSTIC AND PROGNOSTIC VALUE IN CHILDREN AND IN ADULTS. A. RISI, Riv. di clin. pediat. **28**:98 (Feb.) 1930.

The Vernes reaction depends on a flocculation produced in the blood serum under examination by a resorcin reagent (*Am. Rev. Tuberc.* **15**:500, 1927). It allows a quantitative measurement that is roughly proportional to the severity of the tuberculous infection.

The author made observations with this test in animals and in children and adults. The reaction was obtained at regular intervals during the course of induced tuberculous infection in animals, and was compared with the state of pathologic lesions; the Vernes reaction paralleled the degree of pathology in 84 per cent of the observations.

Children receiving tuberculin therapy gave a positive Vernes reaction, even when the Pirquet test was negative. During the course of measles and pertussis in tuberculous children, the Vernes reaction remained positive. In cases of tuberculous meningitis, the reaction was positive when the tuberculin tests were negative.

In adults, the Vernes test was of value, as it indicated the degree of infection.

The author claims a definite diagnostic and prognostic value for the Vernes reaction.

HIGGINS, Boston.

ON THE PRACTICAL VALUE OF THE TUBERCULIN REACTION OF B. TRAMBUSTI. B. DELUCAS, Riv. di clin. pediat. **28**:227 (March) 1930.

The tuberculin reaction of Trambusti is the intradermal test. Comparative parallel observations were made on 200 children by means of the (1) Pirquet, (2) Trambusti and (3) Mantoux tests; 22 per cent of the children gave a positive Pirquet test, 56.5 per cent a positive Trambusti test and 62.5 per cent a positive Mantoux test.

The author concludes that the Trambusti test, by reason of its simplicity, should replace the Pirquet test in practice.

HIGGINS, Boston.

THE ANTI-ALPHA VACCINE OF FERRAN. MARTÍNEZ VARGAS, Med. de los niños **30**:343 (Nov.) 1929.

This preparation contains the live virus of tuberculosis and is used both as a therapeutic and as a prophylactic agent. Ferran discovered the tubercle bacillus known as the alpha strain; Koch bacillus is the beta strain. In the same issue of this publication the death of Dr. Jaime Ferran is announced. He was one of Spain's foremost medical investigators and is credited with the discovery of specific vaccines against cholera, bubonic plague and tuberculosis. Ferran discovered the alpha and epsilon types of tubercle bacilli and his were better known than Koch's beta and gamma strains. He inoculated 680 children, from 3 months to 3 years of age, with the vaccine, and only one developed active tuberculosis. In Valencia, 1,900 children were inoculated without any severe reactions. Two children with active tuberculous pneumonia were given three injections each; the results were excellent, and the children grew up without further trouble. In South America, fifty children in one group were vaccinated, and over a long period of observation none has acquired tuberculosis. In Mexico and the Argentine, the vaccine is used frequently, without severe reactions.

This vaccine contains the bacillus, with its endotoxins and exotoxins. A slight rise in temperature follows, although rarely more than 1 C. Renal tuberculosis is a contraindication. It is advisable to give the vaccine early in life because tuberculosis appears early. It does not cure active tuberculosis, but it has given good results in cases of tuberculosis of the glands and joints. It is also used in asthma and in whooping cough. Ferran attempted to determine why the anti-alpha tuberculosis vaccine had such a favorable effect on cases of whooping cough.

Although whooping cough is due to the Bordet-Gengou bacillus, he says that it is a pretuberculosis catarrh and consequently responds to antituberculosis vaccine.

DWYER, Kansas City, Mo.

COD LIVER OIL IN THE TREATMENT FOR CONGENITAL SYPHILIS. E. KOBLIGK, Med. Klin. **26**:516 (April 4) 1930.

The author recommends as a routine treatment the administration of cod liver oil to all children with congenital syphilis. He not only believes in the prevention and cure of rickets in these children, but thinks that cod liver oil actually helps the action of antisyphilitic drugs as a tonic and a roborant.

ZENTAY, St. Louis.

THE TREATMENT FOR OPEN PULMONARY TUBERCULOSIS WITH VITAMIN D (VIOSTEROL). H. MENSCHEL, München. med. Wchnschr. **77**:239 (Feb. 7) 1930.

Menschel reports good results in the treatment for tuberculosis with concentrated viosterol. Most of the fifty-eight patients were adults who were under treatment with viosterol for six to twelve months. Roentgenograms and physical signs indicate that exudative processes in the lungs were absorbed and that there was healing in many cases by scar formation in from four to six months. The incidence of pulmonary hemorrhage was greatly reduced. The patients expectorated less, their temperature was lower and they gained in weight. The diazo reaction changed from positive to negative during the treatment. Tuberculosis of the bones, larynx and skin also showed a tendency to heal. Twelve of the sixteen cases of laryngeal tuberculosis showed improvement in from one to two months. There was no change in cases of intestinal tuberculosis. There was no improvement in the secondary anemia, which was, however benefited by liver and arsenic therapy. Large doses of viosterol (16 mg., three times daily) caused vomiting, leukocytosis, anorexia and loss of weight. Injury to the kidney was not observed. The therapeutic dosage is five drops of a 1 per cent solution of viosterol once or twice daily.

BRAHDY, Mount Vernon, N. Y.

Internal Diseases

DEPRESSED BONE-MARROW FUNCTION FROM THE ARSPHENAMINES (INCLUDING A TYPE OF SO-CALLED AGRANULOCYTOSIS). D. L. FARLEY, Am. J. M. Sc. **179**:214 (Feb.) 1930.

Depressed bone-marrow function from arsphenamines is a rare condition and is considered in the sense of including many cases of changes in the blood after the administration of arsphenamine, such as aplastic anemia, purpura hemorrhagica and agranulocytic angina. It is probable that the changes are due to some congenital defect in the hematopoietic system which may be revealed only by some chance secondary infection, which also probably plays a great part in the production of the usual fatal outcome.

All forms of arsphenamine are equally liable to produce the depression, and no further treatment should be given to any patient showing early signs of bone-marrow depression. While the most accurate check is made by blood counts, other symptoms may be fever or malaise, a mild macular or papular itchy exanthema or purpura.

Arsphenamine therapy may be resumed cautiously if the patient is well and free from blood changes after one year.

For acute symptoms sodium thiosulphate should be given intravenously as early as possible. Blood transfusions should also be employed and repeated frequently enough to tide the patient over the depression stage.

JAMIESON, Detroit.

A Case of Congenital Hemolytic Jaundice with an Unusually High Percentage of Reticulocytes. James M. Baty, Am. J. M. Sc. **179**:546 (April) 1930.

The author reports in detail a case of congenital hemolyitic jaundice in a white boy, aged 3. He includes a graphic chart of observations on the blood over a period of two years, showing the observations prior to splenectomy as well as following the operation. The unusual feature was the high percentage of reticulocytes over a long period of observation. Two years after removal of the spleen, examination of the blood showed a reticulocyte count of from 30 to 70 per cent, persistence of the increase of percentage of immature red blood cells, jaundice, anemia and occurrence of hemolytic crises or indications of continued activity of the disease process.

Henske, Omaha.

Carcinoma of the Female Genital Tract in Childhood. Arthur H. Morse, Am. J. Obst. & Gynec. **19**:520 (April) 1930.

The author has reviewed the literature dealing with epithelial neoplasms in children. He gives a brief review of the eight cases reported, only three of which are complete enough to be definite.

The case reported by the writer is that of a girl, aged 10 years, who complained of a profuse vaginal discharge that at times was tinged with blood and contained bits of necrotic tissue. A diagnosis of gonorrheal vaginitis had been made by the family physician. For three weeks after her admission to the hospital, irrigations were given for this condition. Later, investigation under gas anesthesia revealed friable tissue and fixation at the cervix. Laparotomy was performed in an attempt to remove a uterus that was enlarged to five times its normal size. Owing to adhesions of the intestine and friability of the tissue, only tissue for microscopic examination was removed, and the abdomen was closed. Ten months later, the patient died suddenly. Autopsy was not permitted.

Allen, Chicago.

Congenital Capillary Angioma of the Parotid Gland. Joseph McFarland, Arch. Path. **9**:820 (April) 1930.

A swelling in the left parotid region had been present in an infant from birth. It increased rapidly in size, and at 5 months of age the child was brought for operation. A flattened, encapsulated, distinctly lobulated mass resembling a hypertrophied parotid gland was removed. Microscopic examination showed, however, that an excess of capillaries had developed at the expense of the glandular tissue. Thirty-three similar cases are cited. Surgical removal of the entire gland is the operation of choice, and in no case has a recurrence been reported.

Leslie, Evanston, Ill.

Pyloric Stenosis in Mother and Infant. Leslie O. Ashton, Arch. Pediat. **46**:651 (Oct.) 1929.

On the tenth day of a male infant's life, symptoms of pyloric stenosis became marked. Projectile vomiting began on the seventeenth day. Gastro-enterostomy was performed on the mother, and a Rammstedt operation on the son.

Wilson, Norfolk, Va.

Systolic Blood Pressure in Early Infancy. Lotta V. Wolff, Arch. Pediat. **47**:165 (March) 1930.

A simple method for taking blood pressure in infancy is described, with some results of examinations of cumulative blood pressure examinations of sixty normal infants during the first six months of life are presented. The arithmetical

average for the systolic pressure rises gradually from 62 at birth to 74 at 6 months. A number of individual variations from the arithmetical average are shown in curve form, the meaning of which cannot be analyzed as yet.

WADDELL, University, Va.

PYOGENIC INFECTIONS ABOUT THE LIVER. JOHN R. BOLING, J. Florida M. A. **16**: 314 (Jan.) 1930.

Any pyogenic infection in the abdomen may cause subphrenic abscess. Infection of the blood stream may give rise to abscesses in or above the liver; most infections occur through the portal stream. A case of abscess following duodenal perforation is reported in a boy aged 15, and another in a boy aged 6, following septicemia from infection of the arm.

BIEKER, St. Petersburg, Fla.

BRONCHIAL ASTHMA. C. J. HEINBERG, J. Florida M. A. **16**:451 (April) 1930.

Attention is called to the preponderance of allergy in cases of asthma, with focal infection and protein putrefaction as common causes.

BIEKER, St. Petersburg, Fla.

CLINICAL PICTURE OF HYDRONEPHROSIS IN CHILDREN AND YOUNG ADULTS. W. C. QUIMBY, South. M. J. **23**:328 (April) 1930.

Hydronephrosis occurring in childhood and youth is due to a special cause and results in a definite clinical picture. The author believes that some factor which interferes with the dynamics of the ureter is the fundamental cause. It is closely tied up with the vascular supply of such a kidney.

The diagnosis is easy, if the condition is suspected. Prompt diagnosis followed by operation will often save the kidney. Delay will allow it to be destroyed.

SCHULTZ, Chicago.

A CASE OF CELIAC DISEASE. LEWIS THATCHER, Edinburgh M. J. (Tr. Med.-Chir. Soc.) **37**:34 (April) 1930.

A girl, aged 4 years, had a history of an indefinite illness beginning at the age of 2, the symptoms being progressive weakness, loss of appetite and the passage of large foul stools. The size of the abdomen steadily increased. She spent sometime in the hospital, and the diarrhea stopped. Invalidism, inability to sit up well and finally deformity of the chest and spine appeared. At 4 years of age she was the height of a child of 2, and her weight that of a child aged 1.

Her osseous system became generally deformed. This can be understood because of the low amount of calcium in the blood and the definite rachitic changes in the wrists. Roentgenogically she has begun to improve; she could take oragne juice, cod liver oil and dried fat-free milk well. During this period of improvement, she gained 2 inches (5.1 cm.) in height within a few weeks.

NEFF, Kansas City, Mo.

RENAL DWARFISM. E. A. COCKAYNE, Proc. Roy. Soc. Med. **23**:259 (Jan.) 1930.

A case of renal dwarfism was reported in a boy, aged 5½ years. He weighed 32 pounds (14.5 Kg.) and was small in height. The epiphyses of the long bones were thickened and broadened. The heart was not enlarged. Urinalysis showed no casts or pus; albumin was present. Blood urea was 112, nonprotein nitrogen 78.4, calcium 8.4 and phosphorus 5.38 per cent.

WILLIAMSON, New Orleans.

CYANOSIS AND FINGER CLUBBING WITHOUT DEMONSTRABLE CAUSE. WILFRID SHELDON, Proc. Roy. Soc. Med. **23**:264 (Jan.) 1930.

A boy, aged 9 years, was in good health until the age of 7 years, when he gradually became cyanotic and short of breath. His mother stated that she had noticed the clubbing of the fingers when the patient was a baby. A roentgenogram of the chest showed the heart to be normal in size; the electrocardiogram was normal. Examination of the blood showed: red blood cells, 7,580,000; hemoglobin, 140 per cent, color-index, 0.9, and white cells, 12,500. The Wassermann reaction was negative. The author felt that the most likely explanation of the symptoms was some congenital abnormality of the heart or main vessels, and suggested that it might be a patency of the interventricular septum.

WILLIAMSON, New Orleans.

CAT ASTHMA (TREATED). P. D'ARCY HART, Proc. Roy. Soc. Med. **23**:265 (Jan.) 1930.

A boy, aged 7 years, gave a history of asthma for two years. No family history of asthma was obtainable. A skin test showed a marked positive reaction to cat hair and a slight positive reaction to dog hair; negative results were obtained with all other substances tried. He was given increasing doses of cat extract subcutaneously at intervals of an hour and a half; after a maximum dose of 85,000 units had been reached—in three days—the boy was discharged. He was observed for three months and did not have another attack of asthma, although he played with a cat daily. The skin reaction, however, was still positive to cat hair, and negative to other substances.

WILLIAMSON, New Orleans.

ACUTE COLLAPSE OF RIGHT LUNG. J. C. JEWESBURY, Proc. Roy. Soc. Med. **23**: 265 (Jan.) 1930.

A case of acute collapse of the right lung was reported in a girl, aged 7 years. She had suffered from asthma for two years during which time the chest had been examined frequently but no physical signs of disease had been found. When seen on Oct. 20, 1929, she gave a history of wheezing for two days and abdominal pain. The abdomen was normal. The apex beat was in the third right space 1 inch (2.5 cm.) from the right sternal edge. No murmurs were heard. Over the right side of the chest there was moderate dulness and almost cavernous breath sounds. The left side of the chest showed exaggerated breath sounds. Roentgen examination confirmed these observations. By November 4, the apex beat was found in the fourth space about 1¼ inch (3.1 cm.) from the midline. The percussion note was hypersonant over both lungs. The breath sounds over the right lung were weaker than over the left but were normal. The child looked well and had no symptoms. A roentgenogram on November 20 showed that the right lung had completely expanded.

WILLIAMSON, New Orleans.

JUVENILE MYXOEDEMA. R. E. SMITH, Proc. Roy. Soc. Med. **23**:268 (Jan.) 1930.

A case of myxedema was reported in a girl aged 8 years. The mother stated that the condition came after an attack of measles three years previously.

WILLIAMSON, New Orleans.

PERICARDITIS COMPLICATING PNEUMONIA IN INFANCY. P. NOBÉCOURT, Progrès méd **45**:550 (March 29) 1930.

This condition is rare in children under 5 years and even uncommon in those under 10 years. It most frequently follows bronchopneumonia. The cardinal signs

are temperature of around 39 C. (102.2 F.), precordial pain, dyspnea and rapid irregular pulse. The physical signs are increased cardiac dulness, precordial rub and obliteration of the cardiohepatic angle. The prognosis is very poor.

SANFORD, Chicago.

LOBUS VENAE AZYGOS. R. MÜLLER and G. WEBER, Monatschr. f. Kinderh. **46**:403 (March) 1930.

In 1778, Wrisberg described what he called the lobus venae azygos. This consists of a separation of the upper right lobe into two parts by a fissure dug by the azygos veins. For over a hundred years this had only pathologic interest, but in 1927, Velde described the roentgenologic diagnosis. The latter consists of the recognition of a hair line corresponding to the position of the azygos vein, the lower end enlarging to a bead.

The authors describe several cases and submit four interesting plates.

GERSTLEY, Chicago.

Nervous Diseases

PARATYPHOID ENTERITIDIS MENINGITIS: REPORT OF AN ADDITIONAL CASE DUE TO BACILLUS ENTERITIDIS. FRANK B. LYNCH, JR., and SAMUEL A. SHELBURNE, Am. J. M. Sc. **179**:411 (March) 1930.

The author reviews the literature of reported cases and also describes an additional case in detail, which makes the sixteenth case reported. The majority of cases occur in children. All the children 1 year of age or less died, including the one in the case reported. In most of the cases the spinal fluid was purulent or showed a predominance of polymorphonuclear neutrophils. The author states that this condition should be suspected whenever the gram-negative motile rods are found in the cerebrospinal fluid.

HENSKE, Omaha.

THE KETOGENIC DIET IN THE TREATMENT OF CHOREA IN CHILDREN: A PRELIMINARY REPORT. JEROME S. LEOPOLD and JACOB ROTHSTEIN, Arch. Pediat. **46**:593 (Oct.) 1929.

In observing many hundreds of cases of chorea the authors conclude that no form of physical therapy or medication shortened the course of the disease or prevented cardiac complications. Removal of infected tonsils and adenoid tissue made the patient more comfortable but did not shorten the course of chorea or prevent its recurrence or sequellae.

The following procedure was used: The child was weighed every two days. The urine was examined daily for acetone and diacetic acid. Determinations of blood chemistry and carbon dioxide-combining power were made before the child was placed on the ketogenic diet, and they were repeated at weekly intervals. The total caloric needs were based on the normal expected weight of the child for its height. Twenty-five calories per pound of body weight per day approximated the results obtained by adding 50 per cent to the basal requirement. The protein intake was kept as low as was consistent with a positive nitrogen balance; 1.5 Gm. of protein per kilogram of body weight were employed in the diets. The vitamin and mineral salt requirements were met. Salt was not restricted, and no medication was given. The carbohydrate was arbitrarily set at 60 to 100 Gm., depending on the age and weight of the child, the younger children receiving 60 Gm., and the older 80 or 100 Gm. The fat was determined by subtracting from the total calories the sum of the calories contributed by the protein and carbohydrate. The carbohydrate was lowered 10 to 20 Gm. a day until 20 Gm. a day was reached. The protein was kept constant. The carbohydrate was finally lowered to 10 Gm. and the fat raised 45 Gm., with resulting ketosis.

The degree of ketosis produced was apparently sufficient to effect the gradual cessation of the choreiform movements. The ketogenic ratio (Woodyatt's formula) was between 2.5 and 3.5. Twelve patients with chorea were treated; in nine the results were good. The period that elapsed before the development of ketosis was from three to eight days. The period of continuous ketosis required for the disappearance of the choreiform movements was approximately from nine to twenty-four days. In one case of seven months' duration there was no improvement. In some instances the high fat intake may not be well tolerated. There were not significant changes in the blood or in its carbon dioxide-combining power, nor was there well marked clinical acidosis. The authors conclude that the ketogenic diet is of definite value in diminishing and finally causing complete disappearance of choreiform symptoms. The period of rest in bed seems definitely shortened.

WILSON, Norfolk, Va.

SEROUS MENINGITIS. LEON ASTELL, Arch. Pediat. **46**:617 (Oct.) 1929.

A case of serous meningitis with recovery is reported.

The disease may be local or general (diffuse). It may occur in the course of or following general infectious fevers, such as pneumonia, influenza and rheumatism. Cases have been reported following measles and vaccination against smallpox. Trauma may cause it. Toxins (lead, alcohol) or foci of infection adjacent to or remote from the cranium may act as exciting causes. Otitis media is the most frequent cause. The exact nature of the pathologic process is obscure. The spinal fluid, though presenting evidence of meningeal irritation, is free from microorganisms. The diagnosis between serous and septic meningitis is often difficult for the reason that in the latter condition microorganisms are often not found at the first or subsequent examinations of the spinal fluid. The treatment is symptomatic, with an occasional lumbar puncture to relieve intracranial pressure.

WILSON, Norfolk, Va.

ACUTE NON-SUPPURATIVE ENCEPHALITIS COMPLICATING CERTAIN INFECTIOUS DISEASES OF DOUBTFUL ETIOLOGY. LAIRD M. MORRIS and MYRL MORRIS, Arch. Pediat. **47**:135 (March) 1930.

Various forms of encephalitis complicating certain diseases caused by filtrable viruses are grouped together and fully discussed. An attempt is made to show that, from a clinical point of view, these cases are quite dissimilar from epidemic encephalitis, particularly in regard to prognosis. The article is interspersed with case reports and presents an extensive bibliography. It is pointed out that cases of this nature present a sterile spinal fluid in examination by routine cultural methods. The authors express their belief that, clinically at least, encephalitis following parotitis, measles, varicella, variola, vaccinia, typhus and rabies is quite distinct in many respects, and that the etiologic agents are probably dissimilar from that responsible for epidemic encephalitis.

WADDELL, University, Va.

INFANTILE AMAUROTIC FAMILY IDIOCY WITH REPORT OF A CASE IN A CHILD OF NON-JEWISH PARENTAGE. J. N. GREEAR, JR., South. M. J. **23**:324 (April) 1930.

The case of amaurotic family idiocy is reported in white female infant, aged 6 months. Neither parent was of Jewish origin. Birth was normal at full term. Six months after birth the eye changes characteristic of amaurotic idiocy developed. Symptoms of great apathy and fatigue developed at the ninth month and grew progressively worse until death ensued in the tenth month. The characteristic pathologic changes of Tay-Sachs disease were found in the cerebral cortex and in the basal ganglions, the midbrain and the spinal cord. The cerebellum showed the least evidence of the cellular change.

SCHLUTZ, Chicago.

ARREST OF PHYSICAL DEVELOPMENT (WITH RESPIRATORY DYSRHYTHMIA) FOLLOWING EPIDEMIC ENCEPHALITIS. C. WORSTER-DROUGHT and T. R. HILL, Brit. J. Child. Dis. **27**:14 (Jan.-March) 1930.

The authors cite the case of a boy, aged 14, whose weight and height remained stationary after an attack of encephalitis four years previously. He suffered from bouts of noisy tachypnea and displayed behavior disorder though his intelligence was unimpaired. The authors suggest that this condition is analogous to the so-called Lorain type of dyspituitarism.

LANGMANN, New York.

THE TREATMENT OF SPASTIC PARALYSIS IN CHILDREN. F. G. JOHNSTONE, Brit. J. Child. Dis. **27**:17 (Jan.-March) 1930.

If there is a history of a convulsion or if true Rombergism is present, surgical measures are contraindicated.

Stoffel's selective motor nerve resection is the method of choice in all cases. "Stoffel's operations consist in the exposure of main peripheral nerve trunks which give motor nerve supply to the spastic muscles producing the inco-ordination and deformities. The main nerve trunks are exposed proximal to the site of ramification of the motor nerve branches to the muscles under consideration. The motor nerve branches to the respective spastic muscles are carefully dissected and tested. The question then arises how many are to be resected . . . the tendency is to resect too few."

This operation gives excellent results in the lower limbs but comparatively poor ones in the upper.

Retentive splints and reeducation of the muscle groups are important in the after-treatment, but all forms of electrical treatment are absolutely contraindicated.

LANGMANN, New York.

RECOVERY FROM PNEUMOCOCCAL MENINGITIS. HILDA N. STOESSIGER, Brit. J. Child. Dis. **27**:35 (Jan.-March) 1930.

A girl, aged 5 was admitted to the hospital with meningeal signs. Lumbar puncture revealed a turbid cerebrospinal fluid containing over 1,000 polymorphonuclears per cubic millimeter. Gram-positive diplococci resembling pneumococci were seen in the films. No growth was obtained on culture.

The following day, 2 cc. of a 5 per cent solution of mercurochrome-220 soluble was given intrathecally and 2 cc. intravenously, and an intrathecal dose of 4 cc. was given the next day; this was followed by a severe headache. No further treatment was given, and recovery was complete seven days after admission.

As the author admits, this case was not definitely proved of pneumococcic origin.

LANGMANN, New York.

A CASE OF MENINGOCOCCAL MENINGITIS. LEWIS THATCHER, Edinburgh M. J. (Tr. Med.-Chir. Soc.) **37**:35 (April) 1930.

Thatcher showed an infant who at the age of 9 months had evidences of acute intracranial disease. At the first examination no cellular or bacteriologic abnormalities were found. Repeated daily punctures were still negative, as was the ventricular puncture. However, the child continued to be ill and vomited steadily. After being sick four weeks, she became entirely blind; soon after this meningococci were found in the fluid obtained from one of the ventricles, although there was no excess of cells or albumin. She then began to increase in weight. After being kept under observation for three months, her vision began to return. When last seen, her general condition was good except that she was somewhat oversensitive, had twitching habits and possibly had had two slight convulsions. Thatcher fears that secondary hydrocephalus may develop.

The diagnosis in such a case lies between meningitis and encephalitis, but when blindness develops it favors a meningococcal meningitis, in which the amaurosis always disappears; meningococci as well as a low sugar content are found in the cerebrospinal fluid.

NEFF, Kansas City, Mo.

CONSTITUTIONAL MODIFICATIONS IN CHILDREN UNDER THE INFLUENCE OF CLIMATIC CURE. DMITRIEFF, DERNOFF and VASILIEFF, Rev. franç. de pédiat. **5**:483 (Aug.) 1929.

At the sanatarium at Eupatoria during the summer of 1928, eighteen children between 6 and 15 years of age were studied relative to their reactions expressive of a vagotropic or sympatheticotropic type. From this study of the type of dermatographism, the oculocardiac reflex and the response of blood pressure to the injection of epinephrine, the authors conclude that the children undergo a vagotropic reconstruction as a result of the climatic cure. There was a corresponding shift in the leukocyte formula in the direction of a lymphocytosis and an eosinophilia. There was also some depression of the mobilization of blood sugar in response to epinephrine. Studies of the chlorides and uric acid of the blood were inconclusive.

LESLIE, Evanston, Ill.

THE PROBLEM CHILD. H. HANSELMANN, Rev. internat. de l'enf. **9**:118 (Feb.) 1930.

Among the 1,500 children studied, the author cannot ascribe wilful viciousness to a single case; there is always some concealed motive behind delinquency, often closely connected with the child's past and usually centering about his physical status or his environment. The writer finds the latter usually responsible in cases of lying, stealing, laziness and insolence, and it is practically always due to faulty training. If the parents are harsh, narrow-minded and surly, the influence of these characteristics will be disastrous for the growing child.

Educational clinics should be organized for families as well as schools. Teachers may be, and frequently are, entirely ignorant of child training and demand impossible things from children who are physically incapable of meeting scholastic requirements; psychologic and medical examinations should be instituted to determine the capacity of the unusual child.

Hanselmann recommends removal of the problem child from its home to surroundings which would give free play to "soul development." Two types of corporal punishment are discussed: a "short circuit" reaction such as a box on the ear, showing lack of control on the part of the teacher, and the methodical punishment, of more educational value. When the rebellious element is dominant, exclusion from school is the only remedy.

AMESSE, Denver.

THE VEGETATIVE NERVOUS SYSTEM OF THE CHILD. A. DI JEVA, Riv. di clin. pediat. **28**:203 (March) 1930.

The author has assembled twenty-five symptoms indicative of activity of the parasympathetic nervous mechanism (parasympatheticotonic), and twenty symptoms indicative of activity of the sympathetic nervous system (sympatheticotonic). The parasympathetic symptoms include dermatographia, profuse lacrimation and salivation, low body temperature, abdominal pains, enuresis, bradycardia, asthenia and muscular hypotonicity, while the sympathetic symptoms include pallor, diminished lacrimation and sweating, small pupils, exophthalmos, polyuria, hypertonic muscles, tachycardia and, increased blood pressure.

Individual children were subjected to an analysis of the vegetative nervous system by marking the presence or absence of the forty-five symptoms given. The percentages of the twenty-five parasympathetic and the twenty sympathetic symptoms present were determined and afford the basis of evaluating the degree of parasympatheticotonia and sympatheticotonia.

The results of di Jeva's observations are summarized in the accompanying table. Pharmacodynamic tests were not made, but suggestions as to therapy are deductible from the results; thus parasympathetic drugs such as lobelia, belladonna and atropine, or sympathetic drugs such as strychnine, calcium chloride and epinephrine may be indicated.

Analysis of Vegetative Nervous System

	No. Cases	Average Percentage of Symptoms Indicating Activity of	
		Parasympathetic Nerves	Sympathetic Nerves
Normal babies	20	67	33
Normal young children	20	61	40
Normal older children	20	54	46
Rickets	40	71	28
Diphtheritic paralysis	20	70	30
Scarlet fever	15	50	13
Typhoid fever	20	81	18
Tuberculous meningitis	3	85	10
Tuberculous pulmonary glands	20	56	43
Asthma and eczema	10	69	16
Enuresis	1	75	20
Epilepsy	2	41	50
Fröhlich's syndrome	1	61	24
Vomiting	4	81	13
Exophthalmic goiter	1	42	71
Neurosis	2	64	38
Acrodynia	1	45	66
Atropine poisoning	1	0	82
Lipodystrophy	1	8	83

It appears that physiologic parasympatheticotonia diminishes as the infant grows older; the child veers toward sympatheticotonia as it nears puberty. Most of the acute illnesses of childhood result in a relatively increased parasympatheticotonia. Epilepsy, acrodynia and hypothyroidism are accompanied by sympatheticotonia.

HIGGINS, Boston.

A CASE OF THE LATE FORM OF AMAUROTIC IDIOCY WITH ATYPICAL COURSE AND WITH TERMINAL SEVERE DISTURBANCES OF FAT METABOLISM IN THE ENTIRE ORGANISM. H. KUFS, Zschr. f. d. ges. Neurol. u. Psychiat. **122**: 95, 1929.

Kufs points out that there are cases of amaurotic idiocy that for decades show only symptoms of a stationary mental deficiency and are identified with amaurotic idiocy only through the familial history. The symptom-complex of a severe, organic, destructive disease of the brain may develop late in life. Kufs reports a case in which the latter first developed at the age of 36. Necropsy revealed the typical cell changes of amaurotic idiocy spread throughout the brain, but possibly more marked in both frontal lobes. The basal ganglia and cerebellum were markedly involved. The ganglion cells were balloon-shaped, with eccentric nuclei, loss of endocellular fibrils and little disturbance of architecture. Fat stains showed the cells filled with fat. The glia showed regressive and progressive changes. On the other hand, the myelo-architecture of the cortex was but little disturbed. The cerebellum was even more involved than the cerebrum. The entire cerebellar cortex was much smaller than normal, the molecular layer decreased in size and the granular layer thinned out. The next about the Purkinje cells had disappeared, but the myelo-architecture was intact. The Purkinje cells were filled with fat.

other organs in the body were found loaded with lipoid pigments. The cortex of the kidney was filled with fat, especially the tubuli contorti. The capsule and capillary endothelium of the glomeruli were also partially filled with fat. The suprarenals were filled with fat. The connective tissue cells and follicle epithelium of the thyroid, as well as the mesenteric lymph glands and the liver were loaded with lipoids. In the latter, the Kupffer cells in particular were filled with fat. The spleen, on the other hand, showed only a mild fatty infiltration. The heart and pancreas were quite severely involved.

Pick's theory that in splenohepatomegaly there is a primary metabolic disturbance that leads to a saturation of the blood and tissue juices with lipoids, so that the natural depots of neutral fat disappear with the progression of the disease, is fully substantiated by the case of Kuts. Furthermore, the conception of Bielschowsky and Pick that infantile amaurotic idiocy is a part of a disease of the entire organism, designated as a heredofamilial disturbance of the lipoid metabolism, holds true in Kut's case of late amaurotic idiocy. In the infantile form, however, the lipoid cell splenohepatomegaly begins in the first month of life and leads to death in the second year. In Kut's case of late amaurotic idiocy, the disturbance in fat metabolism developed at the end of the thirty ninth year and persisted for two years as a severe marasmus. The fat in the cells in the late form differs from that in the infantile form in that the characteristic large lipoidophages are lacking except in the lymph glands. This rich development of lipoidophages may be characteristic of the infantile as distinct from the late form of amaurotic idiocy.

ALPERS, Philadelphia.

A SYMPTOM OF CHOREA. W. STOELTZNER, Ztschr. f. Kinderh. **48**:124, 1929.

When a child with chorea is asked to take a breath he will open his mouth instead of breathing in. This is to be looked on as an expression of the disturbance of coordination.

EMERSON, Boston.

CROTALIN AND COBRIN IN THE TREATMENT FOR EPILEPSY. J. STUCHLÍK, Časop. lék. česk. **66**:1961 (Dec. 23) 1927.

The author verifies the results obtained by Fackenheim. Crotalin lowers the oxyhemaglobin, destroys red and white cells and increases the precipitation, these factors being an index of relief from symptoms. Crotalin has a neurotoxic and a hemolytic factor, both of which are readily isolated. In the series of patients treated with complex crotalin, definite improvement occurred in 60 per cent, slight improvement in 20 per cent and no change or slight aggravation in 20 per cent. Cases improved by salamandrin were also improved by neurotoxic cobrin, while cases not improved by either salamanderin or complex cobrin were improved by complex crotalin. Complex crotalin produced improvement in 80 per cent, complex cobrin in 23 per cent and neurotoxic cobrin in 85 per cent.

STUCHLÍK, Chicago.

Diseases of the Eye

CONJUNCTIVITIS AS A TRICHOPHYTIDE MANIFESTATION. I. MUENDE, Brit. J. Dermat. **42**:26 (Jan.) 1930.

A case is described in a boy, aged 10, who had a tineal infection of the scalp with associated lesions on the neck and body. The trichophytin reaction was almost negative. Sixteen days after roentgen epilation, a generalized, varicelliform trichophytide and an acute conjunctivitis that simulated Calmette's reaction as seen in scrofulous patients developed. Both subsided within fifteen days, but there followed in about eight days another generalized eruption of urticarial type, but the conjunctivae remained free. The trichophytin reaction made two days after the appearance of the second eruption was strongly positive and there was a focal reaction. The body lesions assumed the characteristics of lichen trichophyticus and another area of infiltration with pus formation on the scalp developed.

Muende concludes that conjunctivitis may develop as an allergic phenomenon in association with a generalized trichophytide in a patient with a deep-seated inflammatory trichophyton infection, just as it does in a tuberculous patient.

WIEN, Chicago.

A CASE OF BUPHTHALMIA WITH NORMAL UNAIDED VISION. J. H. DOGGART, Brit. J. Ophth. **14**:229 (May) 1930.

A boy, aged 10 years, had corneas measuring 13.5 mm. in diameter. Vision in each eye unaided equaled 6/6, and ability to read Jaeger's test type no. 1. In every other respect the eyes were normal, except for an anomaly of the central artery of the retina in the right eye. The central artery was invisible, but its arterial branches radiated from the edge of the disk. The paternal uncle of the patient's mother has a son whose four children were all said to have very large corneas.

The author discusses the classification of such cases. He points out that Kayser, Seefelder and Collins believe that they should be considered as megalocornea, but he prefers to designate them as buphthalmia, because he thinks it improbable that there is any sharp line of division between the two conditions.

ZENTMAYER, Philadelphia.

A CASE OF BILATERAL BUPHTHALMIA WITH MULTIPLE CONGENITAL ABNORMALITIES IN ONE EYE. G. G. PEYMAN, Brit. J. Ophth. **14**:232 (May) 1930.

Buphthalmia of an advanced degree was present in both eyes of a boy, aged 6 years, who suffered intensely from photophobia. In the left eye besides there was almost complete aniridia. There was a rim of rudimentary iris, which at 11 o'clock was wider, from the anterior surface of which a strip of white anterior vascular sheath remnant, with some vessels on its surface, ran to the center of the anterior surface of the lens. The edge of the lens below presented a double coloboma, the suspensory ligament being absent in that region.

Both eyes were trephined. The tension was greatly improved thereby in the right eye, but no change was effected in the left. The author attributes the photophobia to the aniridia in the left eye.

ZENTMAYER, Philadelphia.

TREATMENT OF ACUTE PURULENT OPHTHALMIA OF GONOCOCCAL ORIGIN. R. P. WILSON, Giza Mem. Hosp., Cairo, 3d Ann. Rep., 1928, p. 60.

It was pointed out that in Egypt the principal cause of blindness is undoubtedly gonococcal ophthalmia and not trachoma. The usual treatment is to wash the eyes with perchloride of mercury, 1:5,000, and afterward to paint the conjunctiva with silver nitrate, 2 per cent. For the remainder of the morning, the mother bathes the eyes of the child with a weak solution of potassium permanganate. For the past year, special methods have been employed. Injections of milk were used on eight patients. No patients developed corneal complications. The severe cases responded as well as the milder ones. All discharge and swelling disappeared within an average of three days. Nine patients were treated with antidiphtheritic serum. The dosage was 8 cc. of serum, from one to seven injections being made. All discharge and swelling disappeared within an average of six and six-tenths days.

Thirteen patients were treated by injections of S. V. M. 36 (the symmetrical urea of meta-benzoyl, meta-amino-naphthol, 3-6, and sodium sulphonate). The average dose was 0.01 Gm. The number of injections was from one to five. All discharge and swelling disappeared within an average of six and four-tenths days.

When milk was used, the results were uniform, with strikingly rapid disappearance of the symptoms. The time required for a cure was shorter than in any case by any other method. In all special methods, the usual routine local treatment was used. The conclusion was drawn that for routine treatment, except in case of milk therapy, no real advantage is gained by any of the aforementioned special methods.

ZENTMAYER, Philadelphia.

OBSERVATIONS ON THE RETINAL VESSELS OF FEEBLEMINDED CHILDREN. H. GAUSS, Arch. f. Psychiat. **88**:776, 1929.

The author reports the results of a study of the retinal vessels in 122 feebleminded children. This study was undertaken to check the reports by Jaensch and his co-workers of changes in these vessels as corresponding to deviations in the capillaries in other organs of feebleminded persons. Sixty-nine of the children were boys and fifty-three girls. The diagnoses made were: morons, forty-one and imbeciles, eighty-one. Three of the patients were low grade imbeciles and there were two cases of Mongolian idiocy.

The observations included photographic pictures of the retinal vessels, ophthalmoscopic examinations and examinations of the movements of the extra-ocular and intra-ocular muscles. Depending on the shape of the vessels, the children were divided into eight groups: (1) with normal vessels; (2) with slight variations from the normal; (3) with marked tortuosity of both arteries and veins; (4) with moderate tortuosity of the vessels; (5) with tortuosity of the arteries only; (6) with tortuosity of the arteries and slight deviation of the veins; (7) with tortuosity of the veins only, and (8) with tortuosity of the veins and slight deviations in the arteries. The results were as follows: forty-eight cases belong to group 1, forty-four cases to group 2, two cases to group 3, thirteen cases to group 4, five cases to group 5, two cases to group 6, seven cases to group 7 and one case to group 8.

The author comes to the following conclusions: In a comparative examination of the retinal vessels of normal and feebleminded persons, no definite differences between the two could be found. The feebleminded children showed 25 per cent of definite deviations as compared with 30 per cent of such deviations in normal persons. The individual deviations from normal found in the vessels were certainly acquired after birth in some cases, whereas in the others they were so slight that they could not be considered as significant of a special type of constitution in these children. The results of this study therefore contradict the reports of Jaensch and his co-workers. In accordance with observations made by a large number of investigators, deviations in other parts of the eyes were found frequently, such as errors in refraction, pseudoneuritis, strabismus, maldevelopments and pallor of the disks.

MALAMUD, Iowa City.

HUMAN LENS WITHOUT NUCLEUS, A HITHERTO UNKNOWN MALFORMATION. F. SALZER, Klin. Monatsbl. f. Augenh. **84**:52 (Jan.) 1930.

In a woman, aged 45, vision had been greatly reduced since childhood by corneal opacities of both eyes. An artificial coloboma downward and to the nasal side allowed her to read ordinary print with her right eye without glasses by tilting her head backward. This eye showed red fundus reflex and a round shadow, measuring about one third of the diameter of the iris, in the center of the pupil. The upright virtual picture of the fundus was clearly visible through this area. The margin of the lens appeared in the coloboma.

The slit-lamp revealed some opacities of the anterior cortical, then an apparently empty space in lieu of the nucleus, then the posterior cortical, the posterior capsule and the structure of the vitreous. No crystals or other elements could be detected in the central cavity of the lens; no remnants of the hyaloid artery were present. The patient's vision was 5/15 with a convex glass of 11 diopters, and she could see the finest print at 30 cm. with a 14 diopter lens.

Fischer's description of vacuoles in the eyes of human embryos may be mentioned in this connection, although neither his cases nor those described by Hess and by Seefelder present clear vacuoles and a clear cortical shell like Salzer's case.

STOLL, Cincinnati.

PHENOBARBITAL IN OPERATIONS ON THE EYES IN CHILDREN. H. MEYER, Klin. Monatsbl. f. Augenh. **84**:69 (Jan.) 1930.

The author describes the satisfactory results of the use of phenobarbital in Axenfeld's hospital. Internal doses of from 0.1 to 0.15 Gm. are given twice daily

for the after-treatment of nervous adult patients. It has been used in children during the last year in the following doses: 0.02 Gm. for children aged 4 months, 0.05 Gm. for those aged 1 year, 0.06 Gm. for those aged 2 years, 0.09 Gm. for those aged 5 years, 0.1 Gm. for those aged 6 years and 0.15 Gm. for those aged 12 years. Phenobarbital is administered while the patients are still in bed, an hour prior to the operation. The children offer no resistance when so put on the operating table, with the result that exact examinations can be made, or they can be placed properly for irradiation; local anesthesia and other preparations are facilitated in extirpation of the tear sac, in enucleation, in tenotomy and in smaller plastic operations on the lids or the conjunctiva. The administration of phenobarbital preceding a short ethyl chloride narcosis is sufficient for tonometry in hydrophthalmos, discission of congenital cataracts and iridectomy; it reduces the quantity of ether required for trephining in buphthalmos, complicated iridectomies, linear extraction, magnet extraction and more complicated plastic operations; it also lessens the frequency of vomiting after operations.

STOLL, Cincinnati.

Diseases of the Ear, Nose and Throat

NASAL SINUS DISEASE IN SMALL CHILDREN. L. W. DEAN, Laryngoscope **50**:371 (May) 1930.

In considering the etiology of this condition, it should be pointed out that various investigators have concluded that one must look beyond the presence of the infectious organism to ascertain the real cause of infection. The situation was considerably clarified when Shurley demonstrated that the degree of infection was determined by the virulence of the organism plus the resistance of the cell. Deficient diet, poor hygiene, allergy, metabolic disturbances, climatic conditions, swimming, endocrine disturbances, nephrosis, diseased tonsils and adenoids, nasal blockage and infection, especially in contagious disease, are among the etiologic factors listed by the author as being concerned with sinus disease in children. Deficiency in vitamins, especially vitamin A, is of great importance, but it must be kept in mind that while a diet rich in vitamin A is essential in the treatment for sinus disease, it does not take the place of proper laryngologic treatment. This must accompany the dietary therapy.

The allergic nose must be watched for in children as well as in adults. These patients are frequently operated on unnecessarily, but it must be kept in mind that a suppurative sinusitis and an allergic condition may be present in the same instance. The author stresses the value of examining the nasal discharge for the presence of a possible eosinophilia. He states that an eosinophilia of 10 per cent or more in the nasal discharge indicates allergy. It is thought that allergy interferes with ciliary action and causes stagnation in the sinuses with resulting infection, which when once established, may require an operation on the sinus. In such cases asthma frequently results, but is often relieved by treatment for the sinus infection. The patients treated in the author's clinic are those who have polymorphonuclear leukocytes in the nasal discharge. They have a history of an infection of the upper respiratory tract accompanied by asthmatic attacks. Vaccines and allergic treatments do not give a satisfactory result. There is evidence of sinus disease, and the polymorphonuclear cells are in the discharge during the acute attack. It is the constant appearance of evidence of infection in the sinuses at the time of the asthmatic attacks that allows one to predict a satisfactory result if the sinusitis is eradicated.

The diagnosis of sinus disease in children is often extremely difficult. There may be no nasal discharge, but simply malnutrition, a slight leukocytosis, sometimes a little fever and a history of preceding colds or influenza. The author believes that every child with a disturbance of the upper respiratory tract, followed by fever in which no demonstrable condition of the ears or lungs is responsible, should be considered as probably having a case of residual sinusitis.

The pathologic changes of nasal sinusitis in small children differ from those of the adult in that the changes due to marked chronicity are less marked. The septal walls of the ethmoidal cells are often roughened owing to absorption of the bone. There may be thickened periosteum, subperiosteal abscesses and mucous membranic lining, which is much thickened and infiltrated with inflammatory cells. The cilia may be destroyed. Polypi formation may be present, and granulation tissue is common.

The first step in the treatment for the condition is the eradication of the cause. The diet, allergy, endocrine disturbances and all systemic etiologic factors must be considered, and a thorough examination by a pediatrician is essential in order to get a complete report on these conditions. The eradication of the predisposing factors, pediatric and laryngologic, together with the most simple local treatment, will control satisfactorily nine tenths of all cases of chronic nasal sinusitis in children without any operative work on the sinuses. These children should live a normal existence with plenty of outdoor life. Diseased tonsils and adenoids, if present, should be removed. Operations on the nasal sinuses of children, other than meatal drainage of the maxillary sinuses, are rarely indicated.

SNAPP, Grand Rapids, Mich.

OTOLOGY IN CHILDREN. E. MARTIN FREUND, M. J. & Rec. **131**:342 (April 2) 1930.

Otoscopic observations in infants and young children are often undefined and atypical. Secondary infections (otitic) occur often in infants and young children, especially associated with exanthemas, paranasal sinusitis, influenza and pneumonia, as well as with acute gastritis. Sinus infections are much more prevalent in children than commonly believed; by their tendency to chronicity, they often lead to deafness or marked disturbances in hearing. Aside from differences in developmental time, chronic diseases of the middle ear manifest themselves no differently in children than in adults, except in intensity, reacting more severely in the young child. In young children the temperature is not a reliable criterion as to the degree of involvement of the middle ear. On the contrary, the duration and character indicate the severity of the infection present. Vomiting, especially in the presence of irritability and fever, may be an indication of the presence of an infection of the middle ear, a mastoid inflammation or both. Close cooperation between the otologist, the clinician and the pediatrician is conducive to better results in the handling of otitic diseases of children and infants.

WILLIAMSON, New Orleans.

TONSILLECTOMY BY DIATHERMY USING SURFACE ANAESTHESIA. WARNER COLLINS, Lancet **1**:859 (April 19) 1930.

The advantages of diathermy as cited by the author are: 1. It needs no general anesthesia. 2. It causes no shock of any kind. 3. It entirely eradicates the tonsil. 4. It carries no risk of hemorrhage, primary or secondary.

The largest tonsil can be treated from two points of application while the majority can be destroyed as one single unit. The author describes the technic of the operation in detail and remarks that he does not think the method suitable to children under 14 years of age.

The process described is strictly a combination of true diathermy and fulguration. The operation is said to be practically painless.

LANGMANN, New York.

Diseases of the Skin

ARSENIC FINDINGS IN ECZEMA AND ALLIED CONDITIONS IN INFANTS AND YOUNG CHILDREN. L. S. VAN DYCK, BINFORD THRONE and C. N. MYERS, Arch. Pediat. **47**:218 (April) 1930.

Specimens of urine from 105 infants and young children with eczema or with urticaria were examined for arsenic. In fifty instances no arsenic was found. In

the other fifty-five cases, arsenic was found in amounts ranging from 0.04 to 2.3 mg. per hundred grams of dried specimen. Eleven controls were negative for arsenic except one, and this was a patient who had received thallium acetate.

Specimens of breast milk from mothers who were nursing babies with eczema contained arsenic in forty of fifty-five patients examined.

Clinical improvement was noted following the administration of sodium thiosulphate. The drug was given in phenylsalicylate coated tablets of 2½ grains (0.16 Gm.) each, three times a day before meals. In some instances it seems to be almost a specific.

WADDELL, University, Va.

SOME OBSERVATIONS ON THE CAUSATION OF ERYTHEMA EXUDATIVUM MULTIFORME (HEBRA). EDWIN RAMEL, Brit. J. Dermat. **42**:11 (Jan.) 1930.

Ramel discusses the rôle of *Streptococcus hemolyticus* in the etiology of erythema multiforme, with references to the literature, and states that he cannot accept the streptococcal theory as an explanation of the etiology. He gives a résumé of the facts previously published by him, in which the Koch bacillus was demonstrated both in the blood (eight cases) and in the lesions (two cases). The present paper deals with four unpublished cases of erythema multiforme which showed a tuberculous bacillemia at the period of onset of the eruption, which was demonstrated by the method of successive inoculations. Detailed reports of the four cases are presented, together with full description of the autopsy observations in the guinea-pigs after each passage of the infection.

A résumé of each case, together with a discussion of the observations in the four cases, is presented, and Ramel summarizes his article as follows: 1. The presence of a tuberculous septicemia has been demonstrated in four cases of idiopathic erythema exudativum multiforme. The cases in question presented no obvious manifestations of tuberculosis. The erythema exudativum multiforme of Hebra is therefore considered to be a nonfollicular type of cutaneous, tuberculous manifestation of hematogenous origin. 2. The tuberculous virus that is the cause of idiopathic erythema multiforme produces only attenuated lesions on guinea-pig inoculation. The animal does not die spontaneously; it merely acts as a carrier of organisms. An inoculation chancre is not produced. The resulting lesions, however, must be tuberculous, for their successive reinoculation into other animals brings about a progressive exaltation in the virulence of the virus after from two to four passages. In addition, the number of acid-fast bacilli found in the lesions increases, and ultimately they may be isolated in culture. 3. Erythema multiforme develops spontaneously, as a rule, and up to the present time this type of eruption has been classified as idiopathic. In other cases a variable determining factor, either physicochemical, toxi-infectious or physiologic precipitates the onset of the eruption. This provocative process is biotropic. A case of erythema multiforme following an erythema solare is reported as illustrative of this phenomenon. The factors determining the onset of erythema multiforme have hitherto been wrongly considered as its cause, and the term "secondary erythema multiforme" has been applied to these cases. Such a type, however, does not exist, and cases which are designated as such either belong to the class of provoked erythema multiforme, or comprise eruptions which have no etiologic or clinical connection with Hebra's erythema. Four photographs and two photomicrographs accompany the article.

WIEN, Chicago.

NEVUS ACNEIFORMIS UNILATERALIS. K. G. COLQUHOUN, Brit. J. Dermat. **42**: 55 (Feb.) 1930.

A case is described in a girl, aged 17, who first presented signs of the condition at the age of 2 years, when several discrete pustules were noted in the middle of the upper part of the left arm which healed leaving scars. Subsequently comedones developed around the original site and the inflammatory process extended so as gradually to involve the greater part of the outer portion of the

upper part of the arm and suprascapular region, embracing the sensory distribution from the fourth, fifth and sixth spinal segments. Simple comedones, easily expressed, and larger ones that left pitted scars when expressed were noted. Suppurative changes in the sebaceous collections, which are painful, when acute, discharge a purulent material when the lesion has matured and after the crust separates leave smooth, oval depressed scars, were described. The literature pertaining to this condition is reviewed briefly. An excellent photograph is presented illustrating the location and character of the process.

WIEN, Chicago.

THE TREATMENT OF RINGWORM OF THE SCALP WITH THALLIUM ACETATE. G. H. PERCIVAL, Brit. J. Dermat. **42**:59 (Feb.) 1930.

The results of thallium medication in fifty cases of ringworm of the scalp are presented. The drug was administered orally in a single dose of 8.5 mg. per kilogram of body weight, followed by the daily application of a 10 per cent sulphur ointment to the scalp. When a good regrowth of hair had taken place, local treatment was suspended for three weeks, at the end of which time the scalp was examined for any evidence of disease. Successful epilation of the scalp occurred in every case in from seventeen to twenty-two days after the administration of the drug. Toxic symptoms occurred between the third and twenty-eighth day in 44 per cent of the cases, and lasted from two to nineteen days. In no cases were the symptoms severe, and few of the patients were even confined to bed. No age period was specially liable to show toxic symptoms. The author feels that the thoroughness of local treatment during the period in which the scalp is completely bald is of first importance in the ultimate cure of the disease, a cure being obtained in 96 per cent of the cases reported here. The local treatment was carried out daily by skilled nurses. The shortest period necessary to obtain a cure was sixty-three days from the date of giving the drug; the longest period was 148 days, and the average period was 107 days. The administration of thyroid extract and calcium chloride, respectively, in two cases did not in any way interfere with the depilating action of thallium, and the calcium content of the serum was found to remain within normal limits following the administration of thallium. A critical discussion of the special action of thallium on the growth of hair, with references to the literature, concludes the article.

WIEN, Chicago.

PITYRIASIS LICHENOIDES ET VARIOLIFORMIS ACUTA. CASE REPORTS. A. C. ROXBURGH, A. M. H. GRAY, G. B. DOWLING and J. E. M. WIGLEY, Proc. Roy. Soc. Med. **23**:351 (Jan.) 1930.

Three men, aged 26, 24 and 15 years, and one girl, aged 5 years and 9 months, presented eruptions that closely resembled each other. There was an eruption on the trunk, arms, thighs, legs and feet, consisting of five types of lesions: (1) macular pink or yellowish-pink spots ranging in size from that of a large pinhead to that of a pea; (2) slightly raised papules of about the same size; (3) papules covered by a squama; (4) papules with hemorrhage in the center, or hemorrhagic scab; (5) papules in the healing stage, with a depressed scar, from which a scab had separated. Only a few of the lesions developed central hemorrhage necrosis. Section taken from a lesion from which a hemorrhage scab was separated showed patchy cellular infiltration throughout the dermis, extending down to the level of the sweat glands, and somewhat densely aggregated around them, elsewhere for the most part around vessels. Polymorphonuclear leukocytes were found in numbers in the infiltrate. A hemorrhage scab could be seen over a regenerating epidermis. The cases resembled parapsoriasis and were subjectively asymptomatic, but cleared up within from four to six months. In one case 4-amino-2-aurothiophenol carbolic acid was employed successfully. Reference was made to Mucha as the author who first described the condition.

GUY, Pittsburgh.

IMPETIGO AND PSORIASIS. L. PÉRIN and C. VRETTAKIS, Bull. Soc. franç. de dermat. et syph. **37**:226 (Feb.) 1930.

The patient, aged 2½ years, had impetigo, and about two and one-half months later psoriasis developed, which seemed to be precipitated by an injection of diphtheria anatoxin. Cultures of the psoriatic scales showed staphylococcus and streptococcus. Intradermal reactions to these organisms were positive. No doubt the terrain plays an important role in psoriasis, but in the present case, the chain of events appeared more as a series of fortuitous circumstances.

MICHAEL, Houston, Texas.

DUHRING'S DISEASE IN AN INFANT, THERAPEUTIC CONSIDERATIONS. P. L. DRONET, Bull. Soc. franç. de dermat. et syph. (Reunion dermat.) **37**:1 (Jan.) 1930.

Dronet's patient was 15 months of age. The eruption was erythematous and bullous. His treatment, which was followed by disappearance of the eruption, consisted in the subcutaneous injection of 1 cc. of the bullous contents. Five injections on alternate days were required.

MICHAEL, Houston, Texas.

Surgery and Orthopedics

CONGENITAL DISLOCATION OF THE HIP. H. A. T. FAIRBANK, Brit. J. Surg. **17**:580, 1930.

The study was founded on thirty-five museum specimens, comprising forty-six dislocated hips and fifty open operations. The primary fault was found to be the poor development of the upper margin of the acetabulum, including malformation of the cotyloid ligament, the cartilaginous margin and even the bone. As the condition progresses the acetabulum later assumes a triangular shape with a sharp, straight and not uncommonly undercut edges, the cavity being filled by cartilage or fibrofatty tissue. Secondary changes include a triangular outline of the obturator foramen and an increase in the pubic angle; the ilium is shorter and broader than normal, and a false acetabulum forms on the dorsum ilii which may be located high, low, anteriorly or close to the sciatic notch. The tuber ischii shows roughening and thickening of the bone. The femoral head is smaller than normal, though relatively larger than the acetabulum, and is flattened on its lower and posterior aspects with erosion and lipping in adults. The femoral neck is usually longer and more slender than normal and is associated with varying degrees of coxa vara. The capsule migrates upward, blends with the periosteum of the acetabulum and becomes thickened. The ligamentum teres is frequently absent in cases of long standing.

LIEVENDAHL, Chicago.

SCOLIOSIS DUE TO ABSENCE OF THE HALVES OF TWO VERTEBRAE. DONALD PATERSON, Proc. Roy. Soc. Med. **23**:271 (Jan.) 1930.

A case of scoliosis was reported in a girl, aged 8 years. In October, 1929, she was first noticed to have spinal curvature. On physical examination, well marked right dorsolumbar curvature and pronounced lumbar lordosis were seen. Roentgen examination showed that the left halves of the tenth and twelfth dorsal vertebrae were absent. There were only ten ribs on the left side, and the eleventh and twelfth ribs on the right side were fused for about 1 inch (2.5 cm.) near their articulation, and there was a deformity of the first lumbar vertebra. The report is accompanied by the roentgenogram.

WILLIAMSON, New Orleans.

CHONDROMA OF FIRST RIB IN CHILD AGED 5 YEARS. CECIL P. G. WAKELEY, Proc. Roy. Soc. Med. **23**:433 (Feb.) 1930.

On examination the patient showed a hard tumor on the right side under the clavicle and attached to the cervical spine. The roentgenogram showed a first rib with a cartilaginous defect in its center. The tumor was purely cartilaginous and did not appear in the roentgenogram. There were no symptoms.

WILLIAMSON, New Orleans.

KOHLER'S DISEASE WITH "MULBERRY" UPPER FEMORAL EPIPHYSES. CECIL P. G. WAKELEY, Proc. Roy. Soc. Med. **23**:600 (March) 1930.

A boy came under observation at the age of 5 because the mother noticed that he had a limp. Roentgen examination revealed curious flattened "mulberry" upper femoral epiphyses and, in the sacrum, a deficiency in the laminae. The knee joints were expanded, but did not show any changes due to rickets. The child appeared somewhat stunted but was very intelligent for his age.

WILLIAMSON, New Orleans.

EIN SICHERE ART IN INFANCY AND CHILDHOOD OF PYELOGRAPHY BY INTRAVENOUS INJECTIONS. RICHARD DRACHTER, München. med. Wchnschr. **77**: 451 (March 14) 1930.

Pyelography by cystoscopy and retrograde injection of the ureters in infants and young children is difficult. Drachter emphasizes the importance of the new method of visualization of the urinary tract by the intravenous injection of contrast mediums. The diagnosis of horse-shoe kidney, congenital absence of one kidney, malformations of the ureter and other abnormalities that at present are found in adult life can be diagnosed in infancy and childhood. The author cites a case in a child, aged 8, with recurrent abdominal pain. Pyelography revealed a double pelvis and ureter on one side, with a constriction of one ureter which caused the symptoms. The roentgenograms in this case and those in a boy, aged 16 months, with a tumor of the kidney are reproduced.

BRADLEY, Mount Vernon, N. Y.

Miscellaneous

SIGMATISMUS. DAVID L. POE, Arch. Pediat. **46**:721 (Dec.) 1929.

The improper production of the friction sounds S, Z, Sh is termed lisping or sigmatismus. Their proper production is dependent on an accurate functioning of the articulation apparatus. There is a detailed description of the mechanics of some of the commoner forms of sigmatismus with illustrative cases.

The importance of early correction of such speech defects is emphasized. Treatment is directed toward making the necessary changes in the position of the tongue with relation to the adjacent portion of the articulation machinery by means of suitable exercises. Imperfect sounds produced by children up to the age of 5 years may be considered physiologic because they are usually due to incomplete development of the muscles concerned in speech. After the age of 6 or 7, imperfect sounds must be regarded as pathologic.

WILSON, Norfolk, Va.

CHANGES IN THE BLOOD CHOLESTEROL IN CHILDREN FOLLOWING INJECTIONS OF HYDROUS WOOL FAT AND IRRADIATION. JEROME S. LEOPOLD and ADOLPH BERNHARD, Arch. Pediat. **46**:756 (Dec.) 1929.

The literature is reviewed. Eleven children, convalescent from various diseases, were studied; determinations of calcium, phosphorus and cholesterol were

made. Hydrous wool fat was rubbed over the entire body. The patients were then exposed to the light from a quartz lamp at a distance of from 27 to 30 inches (68 to 76 cm.) for five minutes. The time of exposure was increased until a maximum of fifteen minutes was reached. The experiment was continued over a period of sixteen days. After ten exposures the calcium, potassium and cholesterol values were again determined. A third series of determinations was made two months after the treatment was begun. The usual mixed diet was given and this was not varied. No attempt was made to give foods supposedly rich in cholesterol. Six of the eleven cases showed a rise in cholesterol ranging from 20 to 80 per cent. In two cases the rise was 10 and 16 per cent, respectively. The greatest rise was seen in a colored child. In one case in which only the ultraviolet light was used there was no increase in cholesterol. Since hydrous wool fat contains a considerable amount of cholesterol and cholesterol esters, the authors conclude that the rise in cholesterol may be due to absorption through the skin. Further studies are being undertaken.

WILSON, Norfolk, Va.

JUVENILE COURTS AND AUXILIARY SERVICE IN FRANCE. OLGA SPITZER, Rev. internat. de l'enf. **9**:287 (April) 1930.

These agencies, now found everywhere in other countries, have developed slowly in France, where but one court, that in Paris, is functioning. It was recognized shortly after the Juvenile Court Act was passed in 1912 that such laws are futile without accessory educational facilities such as social service organizations may provide. These auxiliary forces are now being organized on American lines and are maintained by private grants; they provide suitable care for abandoned, neglected and psychopathic children as well as for those in moral danger. In Paris, a group consisting of one physician, a psychiatrist, seventeen social workers, five secretaries and a considerable number of volunteer women are now assisting the two juvenile judges not only in a comprehensive inquiry into the causes of delinquency but in outlining suitable measures for their prevention.

AMBERG, Denver.

FINDING HOMES FOR UNFORTUNATE CHILDREN IN NORWAY. INGVALD B. CARLSEN, Rev. internat. de l'enf. **9**:301 (April) 1930.

An institution corresponding to the Children's Court in other countries, and known in Norway as the Vergeraad, was established in 1896. It consists of seven members of whom the judge and the local priest are two ex officio. Information concerning cases requiring action of the Vergeraad is furnished by the local police or some interested person, and the resulting investigation may lead to removal of the child from the home to reformatories, educational institutions or a suitable family. In 1926, 59 per cent of the children studied were left with their families, and 41 per cent were removed. Of these, 70 per cent were placed with private persons. The psychiatric adviser of the national board reports that one third of the boys and 6 per cent of the girls so placed later come into conflict with the police. Children boarded out while very young showed the best results. There is a serious lack of schools for the so-called difficult children in Norway, and sustained efforts are now being made to provide such institutions.

AMBERG, Denver.

CHILDREN'S COURT AND THE PREVENTION OF JUVENILE DELINQUENCY IN ENGLAND. HONOR M. MATTHEWS, Rev. internat. de l'enf. **9**:311 (April) 1930.

Children's courts were established in England in 1908. In all but the most serious offenses, they hold jurisdiction over young persons up to the age of 16, the most common charge being theft. The broader aspect of the laws governing

such agencies, especially in the protection of children from dangerous environment, engages the attention of the courts, however, much more than the adjustment of individual cases. To this end, the local educational authorities are consulted, and volunteer organizations, the duty of which embraces the institution of all proper measures for the safeguarding of youth, assist in the care and training of boys and girls assigned to their particular group. Places of detention are provided where children may be studied following remand by the court; these examinations include medical, psychologic and intelligence tests. Probation officers supplement the work of the judiciary and are responsible to the court for children placed in their keeping. Observation homes are needed everywhere to further the efforts of the courts in reclaiming children in moral danger.

AMESSE, Denver.

Society Transactions

AMERICAN PEDIATRIC SOCIETY

JOSEPH BRENNEMANN, M.D., *Presiding*

Forty-Second Annual Meeting, June 17-19, 1930

First Session

June 17, 9 A. M.

CERTAIN ASPECTS OF THE WHITE HOUSE CONFERENCE ON CHILD HEALTH AND PROTECTION. DR. S. MCCLINTOCK HAMILL.

The White House Conference on Child Health and Protection was called by President Hoover because of his intimate knowledge of the problems of child life and the needs for better protection. He requested that the Conference find out what is being done for the health and protection of children, what gaps there are and how they should be filled.

The Conference is organized in four sections: Medical Service, Public Health Service and Administration, Education and Training and The Handicapped. These are in turn divided into committees. Section 1 is comprised of three parts, as follows:

The Committee on Growth and Development is considering the results of laboratory research and making a statistical appraisement of scientifically collected clinical data, thus rendering available knowledge that will be generally useful and practical.

The Committee on Prenatal and Maternal Care is studying obstetric teaching and education, not only of physicians, but of nurses, midwives and lay persons; also the care given to the mother in the prenatal and postpartum periods and to the newly born infant. In addition, the subject of fetal, newly born and maternal morbidity and mortality, and the sciences basic to obstetrics are being scrutinized by this committee to determine what recommendations may be made for reduction in infant and maternal mortality and improvement of the care given to mother and child.

The Committee on Medical Care for Children is dealing with the preventive and curative aspects of the subject. Education of the workers, medical, nursing, social, etc., facilities for the protection of the child's health, and the actual amount of health service obtained by American children are among the topics studied. This committee is allied with the committees in the two last sections of the Conference by a system of liaison which avoids overlapping and provides pediatric opinion whenever needed.

The second section of the Conference is made up of committees on Public Health Organization, Communicable Disease Control, and Milk Production and Control. The third section includes committees on The Family and Parent Education, The Infant and Preschool Child, The School Child, Vocational Guidance and Child Labor, Recreation and Physical Education, and Special Classes. The fourth section consists of committees on State and Local Organizations for the Handicapped, Physically and Mentally Handicapped, Dependency and Delinquency.

The reports of the studies made by the various sections will be issued at a conference to be held in Washington, D. C., in November, and a scientific session also will be held by the Section on Medical Service in February, 1931. A follow-up committee will see to the publishing of the transactions, as well as of special articles and monographs.

The Conference has afforded a unique opportunity for cooperation and better understanding between the groups involved, such as scientists, physicians, dentists,

nurses, social workers, educators, juvenile court workers and many others. It is felt that this has already borne fruit and that a closer relationship will be included in the harvest to be garnered from the year's work.

HYPOTENSION IN CHILDREN. DR. ROWLAND GODFREY FREEMAN.

In my office practice I have observed a group of cases with similar symptoms, showing low blood pressure.

These children are, for the most part, of school age and the parents have sought medical attention on account of the following symptoms: lack of energy, slowness, lack of concentration, indolence, inattention, dreaminess and fatigability.

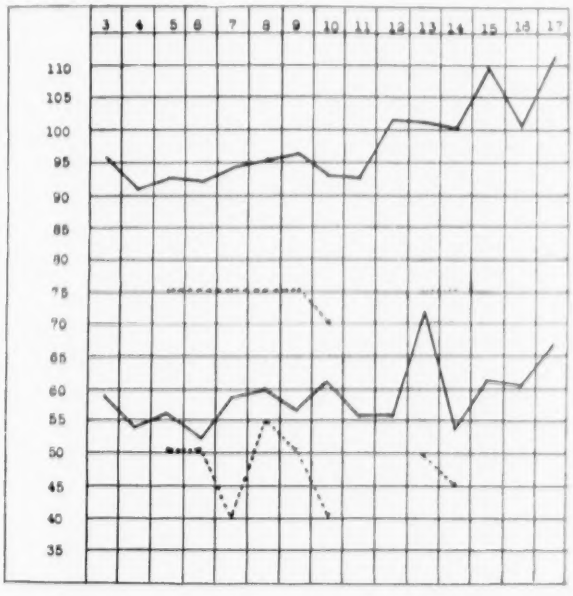


Chart 1.—Average systolic and diastolic blood pressure of normal subjects tested (solid line) compared with low blood pressure (dotted line). In this and chart 2, the horizontal scale indicates age in years, and the vertical scale blood pressure in millimeters of mercury.

Not all children with these symptoms have low blood pressure but many of them do. As the blood pressure increases toward normal the symptoms diminish. The diminution in blood pressure is in both the diastolic and the systolic.

These children are usually fairly well nourished, are apt to be pale and frequently have digestive disturbance.

As a considerable variation in the readings of blood pressure is possible, my readings were all made with a mercury column and a 13 cm. cuff, by auscultation, with the subject sitting in a chair.

The systolic readings were taken with the beginning of a regular beat, the diastolic reading being taken at the lower limit of an audible beat.

Chart 1 shows the readings for 116 consecutive normal subjects, as compared with those for cases of hypotension, which indicate the lowering of both systolic and diastolic pressure.

In order to ascertain whether my readings for my normal subjects corresponded with those of other observers, and in order to ascertain what is normal blood pressure at various ages, I tabulated in chart 2, my own observations on 100 cases, observations on 57 cases at the medical school dispensary by other observers and the observations of Judson and Nicholson, who carefully studied the pressure in 2,300 children. Their chart probably forms the best estimate we have at present of normal blood pressure in children at different ages. Two lines in chart 2 indicate diastolic pressures recorded by Judson and Nicholson, one reading having been taken at the beginning of the dull or fourth phase, and the other when all sound had disappeared.

Although there are statements in medical literature about hypotension in children, I found no reference to this class of cases. In Faber's excellent article,

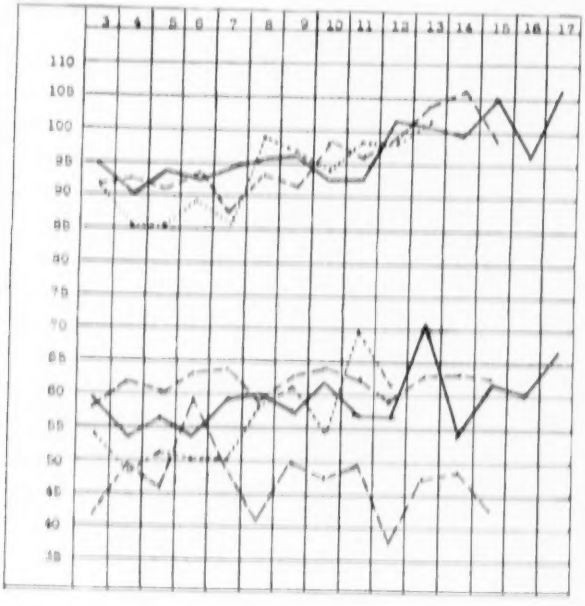


Chart 2.—Blood pressure in normal children: normal children, solid line; patients examined at the Medical School Clinic, dotted line, and 2,300 observations of Judson and Nicholson, dash line.

for instance, he noted the frequent occurrence of hypotension in children and its common occurrence with bronchial asthma; Cushing noted the low arterial tension in hypopituitarism.

These children usually react well to tonic treatment. The administration of pituitary extract or pituitary extract with thyroid is sometimes useful as is the use of tonics of iron and arsenic and strychnine, and the Alpine lamp.

The reports of several illustrative cases were given.

DISCUSSION

DR. J. P. CROZER GRIFFITH: I should like to ask Dr. Freeman a question or two. One realizes that in adults the blood pressure is easily influenced temporarily by outside factors, such as grief, anxiety, excitement, etc. I do not know exactly whether he would attribute the symptoms of this patient to low blood pressure, or the low blood pressure to some other factor which produced the other symptoms as well.

Was he trying to improve the blood pressure with the expectation that the cyst of the symptoms would therefore disappear?

Dr. Charles G. Kerley: Were any observations made on basal metabolism in connection with Dr. Freeman's cases, and did he establish a standard of blood pressure for the various ages of childhood?

Dr. Freeman: In answer to Dr. Griffith, I do not know what relationships these conditions bear. I do not think that these are conditions due to low blood pressure. I think that the low blood pressure is part of the complex. As improvement occurs, the blood pressure increases.

An interesting thing which I did not bring out in the paper is that when the blood pressure is up it seems to stay up.

In answer to Dr. Kerley, no tests of basal metabolism were made. These children were not sick but were brought in to see if their condition could be improved somewhat. They were not given an intensive study.

Severe Jaundice in the New-Born: A Consideration of Sepsis as the Etiologic Factor. Dr. Ethel C. Dunham.

Jaundice in the new-born is an important symptom only when it is severe, progressive and accompanied by other symptoms. A number of clinical entities having jaundice as their chief symptom but of unknown etiology are described in the literature. Such conditions are icterus gravis or congenital familial jaundice, congenital obliteration of the bile ducts and certain diseases manifested by hemorrhage.

Twelve cases of severe jaundice were studied on the pediatric service of the New Haven Hospital. Clinically these cases belonged in one or another of the groups mentioned. The infants were studied with special care to determine whether or not infection played a part in the causation of the illness. Blood cultures were taken in all but one case to determine the presence or absence of sepsis. In infants who died and who were examined post mortem special study was made of the tissues for evidence of infection.

Blood cultures were positive in eight of the twelve cases during life and in one case post mortem. In six cases blood cultures were repeatedly positive with the same organism; in three cases the blood culture was positive on one occasion only. *Bacillus coli* was the organism present in the blood in three cases, in two of which the blood culture was positive more than once. Staphylococci were found in six cases, in four of which the culture was repeatedly positive. Three cases are included in this series in which blood cultures were negative but in spite of which sepsis was suspected on the basis of clinical observations and confirmed in one case by postmortem examination.

The finding of organisms in blood cultures must be carefully interpreted. Blood cultures were considered positive, that is, with evidence of blood stream infection, when the organisms were found in pure culture in broth and poured plates, when they appeared in broth alone after several days' incubation or when colonies were found deep in several poured plates. When the organisms were found repeatedly in pure culture, the evidence in favor of the diagnosis of sepsis was strengthened.

In this group of patients who had jaundice as their major symptom obvious foci of infection were conspicuously absent. This is in marked contrast to a second group of infants under 1 month of age who had sepsis, due in a majority of cases to streptococci, but who showed no jaundice. In this group, ten of fourteen patients had an obvious focus of infection.

My purpose in this paper is to point out the importance of taking blood cultures when infants are jaundiced at or soon after birth or when jaundice is unusually intense or progressive.

It is suggested by this study that sepsis may be the underlying cause of a variety of diseases in the new-born in which jaundice is the chief symptom and of which the etiology has up to the present time been obscure.

DISCUSSION

DR. FREDERIC W. SCHLUTZ: With the various types of organisms, what length of time elapsed before the culture showed growth?

DR. CLIFFORD G. GRULEE: The knowledge of icterus gravis has largely been obtained, I think, from old reports from which there was no adequate means of securing evidence of sepsis.

From what little experience I have had, I am persuaded that icterus gravis is nearly always only a symptom of sepsis, and I think that pediatricians should feel very much indebted to Dr. Dunham for calling attention to the fact that it possibly is an evidence of certain types of sepsis.

The type of sepsis known as nuclear icterus has so far been described in a few cases. The only evidence, so far as I know, of any patient having survived the condition is the evidence that Dr. Dunham has presented.

Recently it was my fortune to see two peculiar types of congenital icterus. Both of these children were seriously affected with icterus at the time of birth. In each case, the observations on the blood were peculiar. In one, the white count was 400,000; on investigation, however, half of this number could be accounted for on the basis of nucleated red cells. There was no disturbance of fragility in these cases, and the blood cultures were negative. Both those children died, the second one before it was possible to obtain an adequate blood test. It is a picture that I have not seen recorded in the literature. It may be that these two represent congenital sepsis rather than a peculiar type of icterus, which has, I think, not previously been described.

DR. HENRY HEIMAN: What type of staphylococcus did Dr. Dunham find? *Staphylococcus albus* is generally considered a contamination, whereas *Staphylococcus aureus* or *viridis* is considered pathogenic.

DR. ISAAC A. ABT: We are indebted to Dr. Dunham for pointing out that icterus and hemorrhage are highly presumptive evidences of sepsis, especially in early life.

Schottmüller recently pointed out that many micro-organisms are capable of producing sepsis at any time of life. It may be one organism or another. There is no specific organism for sepsis. I have several patients with so-called familial icterus, and the outstanding point is that the condition occurred in successive childbirth. The onset was observed about the third day. It is a very fulminating disease. Intense icterus, with perhaps convulsions and vomiting, develops and in a very few days the child dies in extreme collapse.

The course of the disease seems to indicate a perversion of the constitutional state. It seems to be some organic inferiority of the liver itself, instead of septic infection.

The recovery of organisms from the blood is overstressed as a diagnostic factor in septic infection. One may find organisms in the blood and there may be no sepsis, or one may find organisms in the blood in the presence of overwhelming sepsis. The mere presence or absence of organisms in the blood is not the all-determining circumstance.

The most important thing, it seems to me, is the clinical evidence. Chills, fever, sweating, wasting, icterus and hemorrhage are the outstanding manifestations. Pyemia is not common in the sepsis of young infants. Statistics show that 1 per cent of all infants born in large institutions acquire septic infections. Umbilical sepsis is not easy to diagnose. An infant may have an umbilical infection without the condition being recognized. There are no symptoms, no external signs, no evidence of involvement of either the arteries or the vein.

The point brought out by Dr. Dunham is of great value, namely, that icterus and hemorrhage are signs of sepsis in infantile life.

DR. CAMILLE KERESZTURI: Do postmortem observations that are positive for *Bacillus coli* mean necessarily *coli* sepsis to Dr. Dunham, or does she consider in certain cases the possibility of postmortem contamination with *B. coli*?

Dr. Joseph Brennemann: I have always been struck by the fact that so-called physiologic jaundice in the new-born is constant both as to time of occurrence and as to duration, and that jaundice present at birth or occurring later than the third or fourth day is a more serious condition and usually due to sepsis. I rather agree with Dr. Abt that the cases of congenital familial jaundice are not due to sepsis. In one family, three children died apparently of this condition. A fourth one had a bronze-yellow color, and an enormous spleen and liver. This case appeared to be fatal also, but the child recovered without even a blood transfusion.

Not only infants who are yellow at birth or who have jaundice shortly afterward, before the time that ordinary jaundice begins, but those in whom the condition begins at a later time have always interested me. I saw three cases in which jaundice did not begin until the second week or later. Every one of those cases ultimately presented a typical picture of congenital spastic paralysis. In one, there was pyuria, with other evidence of sepsis. I have always thought that those patients had definite sepsis, with probably a complicating encephalitis. In my experience all cases that began late were serious.

Dr. Dunham: A number of the questions that were asked would not have been asked if the charts had been seen. Dr. Schlutz asked regarding the duration of time from the taking of the culture until the growth of the organism appeared. This varied considerably. We thought that when staphylococci appeared after several days' incubation the evidence of a true blood stream invasion was much more conclusive than when the organisms appeared within twenty-four hours. In one case staphylococci appeared in broth five days after the culture was taken. In the other cases in which staphylococci were found the cultures were repeatedly positive.

Dr. Grulee spoke about two infants in whom jaundice was present at birth and whose blood smears showed the presence of many nucleated red blood cells. Two of our cases showed similar blood pictures. I would have discussed these two cases in detail if there had been more time.

Dr. Heiman asked about the type of staphylococcus. Two of our cases showed *staphylococcus albus* and the others *Staphylococcus aureus*. I believe that bacteriologists are not now making as sharp a distinction between *aureus* and *albus* as they used to and that they consider that *S. albus* may be a true blood stream invader.

Dr. Abt spoke of the familial incidence of icterus gravis. Two of the cases that I have reported were in one family. If the patients had died, both would probably have been considered as showing the familial type of congenital icterus.

One point that I am trying to make is that the diagnosis depends a good deal on whether or not the child dies before sufficient time has elapsed to obtain satisfactory data.

Dr. Abt also spoke of the finding of organisms in the blood in the absence of sepsis. I feel that it is probable that one will find organisms, actual blood stream invaders, in the blood of persons who are apparently well. In determining the significance of positive blood cultures one has to take into consideration the clinical course.

Dr. Kereszturi spoke about finding *B. coli* in the blood post mortem. We do not accept the postmortem observation of *B. coli* in the blood as evidence of antemortem infection unless the postmortem culture was made shortly after the death of the child.

Parenteral B.C.G. Vaccination in New York. Dr. Camille Kereszturi, Dr. William H. Park and Dr. Béla Schick.

The advantages of the parenteral over the oral method of vaccination with B.C.G. are: 1. It can be used in patients of any age. 2. The control of the dosage is more exact. 3. In 100 per cent of the cases hypersensitiveness to tuberculin develops, at least temporarily.

We have been using the parenteral method since May, 1929. Since this method has been in use so short a time, we do not attempt to draw conclusions concerning the protective value of the vaccine, but we limit ourselves to the study of the clinical consequences of the parenteral vaccination with B. C. G.

The total number of patients so vaccinated was sixty-one; nineteen of these were vaccinated subcutaneously, and forty-two intradermally.

Of the patients vaccinated subcutaneously, 40 per cent did not show any kind of local reaction; in 60 per cent a characteristic cold abscess developed on the site of the injection, between the fourth and the twenty-sixth week after vaccination. The abscess did not affect the general health of the child, and left a discrete scar of from 6 to 8 mm. in diameter after healing. Of this group, 20 per cent showed enlargement of the lymph nodes on the left side of the groin, corresponding to the left thigh where the injection was given. In one child enlargement of the spleen developed forty-two weeks after vaccination. No definite changes were observed roentgenologically that could be attributed to the vaccination with B. C. G. All the patients in this group gave positive reactions to the Mantoux test between the second and the eleventh week, but four patients lost their hypersensitiveness to tuberculin between the fourth and the ninth month after vaccination. It is probable that, as time goes on, more of the vaccinated children will give negative reactions to the Mantoux test.

Of the patients vaccinated intradermally, 79 per cent showed a local reaction between the first and the eighth week after the vaccine was given. These lesions were similar to a large skin tuberculid, and differed greatly from the cold abscess resulting from the subcutaneous method. We did not notice any definite cold abscess formation in the intradermal group, when the technic was correct; however, if the injection was only slightly deeper than it should have been, a hybrid reaction was produced, with a slight discharge and tuberculoid infiltration. Enlargement of the glands developed in 52 per cent of the cases between the third and the sixteenth week after vaccination. Enlargement of the spleen was seen in 24 per cent of the cases between the third and the eighteenth week after vaccination. No definite changes were noticed in roentgenograms of the chest. All the patients gave positive reactions to the Mantoux test between the second and the tenth week, but nine of them lost their hypersensitiveness to tuberculin from two to ten months after the vaccine was given.

No other signs of tuberculosis were observed in the vaccinated children besides the positive Mantoux test, the local lesion and the occasional enlargement of the glands and the spleen. No death due to tuberculosis occurred.

The total number of revaccinated children was six. They did not show any difference in reaction to the vaccination, as compared with the children vaccinated for the first time.

Summary.—1. Neither the subcutaneous nor the intradermal method of vaccination with B. C. G. seems to be attended with danger. 2. In 100 per cent of the children vaccinated parenterally hypersensitiveness to tuberculin developed at least temporarily. 3. The intradermal method is superior to the subcutaneous because, judging from a rather small number of cases, if the technic is correct, no cold abscess develops.

DISCUSSION

DR. CHARLES HENDEE SMITH: I have been extremely interested in watching this experiment because (1) I am a member of a committee that is concerned with the work that Dr. Kereszturi has carried on, and (2) a great deal of it has been done under my service at Bellevue Hospital.

When the experiment was begun, I was doubtful as to the safety and efficacy. I think that my early skepticism about the value of the oral method was borne out. Too small a proportion of these children acquired a positive Mantoux reaction. The lower death rate in the vaccinated children might be explained on other grounds better follow up, etc. although the controls were carefully watched. At any rate, the oral method was abandoned because it was not certain the bacilli taken by mouth passed through the intestines.

After experiments with parenteral vaccination in Scandinavia and other places, it was decided to try that method. Is it safe? I am not sure whether one can answer that question yet. Some recent reports from Europe have led to a good deal of criticism of the parenteral method. So far, there has been no incident to make one feel that it was not safe. These children do well, but the experiment is not very old. It is possible that some views will have to be modified later. At any rate, it is much safer than putting a child into a tuberculous home unvaccinated.

If the observation made in experiments on animals, that there is no immunity except in the presence of active disease, is true in man, this is perhaps the only hope of protecting children who must be kept in a home with other patients. The statistics for infants, under those circumstances, are so unfavorable that almost anything is justifiable.

The intracutaneous lesion is superficial and apparently harmless. It is much preferable to the cold abscess resulting from the deeper injection. I think that this is a method that is going to last. If the lesion is superficial there is necrosis which disappears quickly and does no harm.

The disappearance of the positive Mantoux reaction is extremely interesting. I have followed that question for a long time with physicians interested in tuberculosis. Few cases have been reported in which a positive tuberculin reaction became negative; these tuberculin reactions were all obtained with the Pirquet method, which is not dependable. I think that all such statistics must be held open to question. I know of no case in which a definitely proved positive Mantoux reaction has become negative in a child who had acquired tuberculosis in the ordinary way. I was extremely skeptical also about the disappearance of the Mantoux reaction in these vaccinated patients. I have seen positive reactions and later negative ones after the use of 10 mg. What does that mean? It may mean that the Calmette bacillus is one with such low virulence that it dies out quickly, which is to be hoped. If one can obtain a negative tuberculin reaction with a complete cure of the disease caused by the Calmette bacillus, I think that one is forced to say that persistence of a positive Mantoux reaction in tuberculosis, as acquired in the usual way, means that the condition never clears up; that is, if a child persistently gives a positive Mantoux reaction he must have some smouldering focus of tuberculosis, no matter how small, somewhere in his body, and that persons with tuberculosis are rarely if ever cured.

Dr. JULIUS H. HESS: Did Dr. Schick's cultures vary in virulence from time to time? I visited Dr. Arvid Wallgren's Hospital at Gothenburg, Sweden, in 1927, at that time he had been making intracutaneous inoculations for about six months. One of his chief concerns was the tendency of his cultures, originally obtained from Calmette, to changes in virulence as related to his animal experiments. Following my visit, his first assistant, Dr. Elsa Lagergren, came to Chicago to work at the Municipal Tuberculosis Sanitarium. She brought some of the culture that Dr. Wallgren had been using, but unfortunately it died out in transit. The only culture of the same strain in America was owned by Dr. William H. Park, and he sent us some of the culture. We found this culture to be highly virulent for both guinea-pigs and rabbits and were afraid to use it; we therefore did no work with it at the Chicago Municipal Tuberculosis Sanitarium. Dr. Lagergren later imported another culture. The person who brought it, however, declared it at New York, and it was confiscated at the customs office.

I should like to ask Dr. Schick whether, in the cases that he observed, the positive Mantoux reactions became negative while the child still had intracutaneous lesions at the site of inoculation or whether they disappeared after the healing of the original lesion.

The thought that I had in mind, from the experience that we had and also from the conclusions of Wallgren, was that one must be careful to test out cultures from time to time in order to make certain that they have not increased in virulence in the subcultures.

DR. ISAAC A. ABT: What does Dr. Schick think about the hypothesis of Petroff which refers to the disassociation of B. C. G. organisms into virulent and nonvirulent groups? Will he also give his opinion about Lange's method of immunization with dead tubercle bacilli?

DR. CAMILLE KERESZTURI: I want to stress that we did not abandon the oral method entirely, but often we found it more convenient to give the vaccine parenterally; this method can be used at any age of the patient, whereas the oral method is limited to new-born infants, i. e., during the first 10 days of life. It is extremely difficult to get the children as early as this. The tuberculin test is positive in a higher percentage of patients vaccinated parenterally than of those to whom vaccine is given by mouth. This fact is significant if the hypersensitiveness to tuberculin and immunity parallel each other. At present, therefore, we experiment with both the enteral and the parenteral methods.

I want to mention Dr. Dolgopol's studies on the blood of children vaccinated with B. C. G. One would expect the greatest changes in the subcutaneous group. To our great surprise, we found that the children given the vaccine orally showed the greatest variations from the normal in the monocyte and lymphocyte ratio. The next group in intensity of reaction was the intradermal and the third group the subcutaneous. This intensive hematologic change indicates that even the oral method is powerful enough to do good or damage.

An observation made by Imamura seems likely to modify our future technic; he found that if he gave intravenously less than 0.01 mg. of B. C. G. to guinea-pigs, he did not obtain immunity, whereas with higher dosage he did.

If his experiments are reliable, our dosages are too low. Probably we will need to increase our dosage to obtain permanent results. If we want to avoid fatalities, the dosage must be increased gradually; in a case reported in the literature, however, 2 mg. was given subcutaneously to a child in whom progressive tuberculosis did not result from such a terrific amount. We probably are far from the dangerous zone, but, at the same time, we wanted to be cautious in increasing the dosage.

Chaussinand advised that one should give two vaccinations at the same time in two different areas of the body. In this way, a smaller number of cold abscesses develops than if he gives the total amount in one place.

It is a pleasure to do this work in this country because the whole medical profession has given full cooperation. Our two main headquarters have been with Dr. Smith and Dr. Bartlett. Those are the places where we first started the work and where we centralized it as much as possible. We have had an especially good opportunity for research in the Bellevue Hospital, where we had three clinics and also ward cases.

There are many biologic problems that could be investigated in connection with this work; for instance, why do certain cases give a local reaction and others do not?

It is also interesting that in some cases, positive Mantoux tests are obtained a week after vaccination, whereas in others, one has to wait eleven or twelve weeks. There is the question of what determines the speed of the reaction in different children. Unfortunately we cannot work out all the problems ourselves and shall welcome any one who comes with cooperative mind and new ideas and is willing to work with us.

DR. SCHICK: We could obtain no direct report about B. C. G. fatalities, but have the reports of Calmette and those printed in *The Journal of the American Medical Association* (Death Following Inoculation with B. C. G. Vaccine, Correspondence **94**:1933 [June 14] 1930). There is no doubt but that these children died of a virulent tuberculous infection. How it happened that the culture became virulent or contaminated, we do not know.

In New York, we personally controlled the cultures; before using them on infants we always checked up on the virulence by animal inoculations. No culture is used before we know the state of virulence, so I think that so far we are secure.

The second question was about Petroff's publication. He found the interesting fact that there are two kinds of tubercle bacilli in our B. C. G. After selecting different subcultures and using special culture mediums he separated smooth and rough colonies. The first one contains very virulent, the second one slightly virulent, bacilli. This fact can be determined only when he uses special culture mediums. There is no case reported in the literature in which smooth colonies became dominant in a human being after vaccination with B. C. G. Of course, in vaccination of human beings with B. C. G. one deals with bovine tuberculosis bacilli —which of course are less virulent for human than for bovine subjects—and one does not increase the virulence of the bacilli either by transfers or by special virulence-increasing mediums. Under these conditions the possibility of stimulation of the virulence is so small that no danger exists.

In connection with the work of Lange, we have no personal experience.

We are considering trying out the dead bacilli. The only question with this method is whether the same intensity of immunity is secured as with living tubercle bacilli. I talked with Lange who was very enthusiastic about his method. We have to wait, however, for further experiments.

I avoided any statement concerning immunity after parenteral vaccination. We have not used this method long enough to be sure about this question.

Dr. Hess asked about the relation between the disappearance of the local lesion and the disappearance of the positive Mantoux reaction. If a scar formation or some remnant of an old lesion is present, it is difficult to decide whether this scar formation has anything to do with the nondisappearance or disappearance of the positive reaction to the tuberculin test. The scar may be marked where the positive Mantoux reaction disappears. My personal opinion is that this relation has to be proved. It is only a hypothesis that as long as there are living bacilli in the system, the positive tuberculin test will not disappear.

I want to repeat that we are just beginning. I pointed out, in the first place, the clinical picture that develops after the parenteral vaccination because this is interesting. It is the first time that we have had an opportunity to study artificial tuberculous infection in human beings. I also would like to thank everybody in New York who helped Dr. Kereszturi, Dr. Park and me. As Dr. Kereszturi said, the cooperation has been wonderful in all the places in which this work has been carried out, particularly in the Bellevue and Fifth Avenue hospitals.

Second Session

Afternoon, June 17

RENAL CHANGES AFTER THE INTRAVENOUS INJECTION OF SUCROSE. DR. HENRY F. HELMHOLZ.

In experiments designed to force bacteria from the blood stream through the kidney into the urine through intense diuresis produced by the injection of hypertonic solutions of sucrose, it was found that characteristic changes in cells of the convoluted tubules were produced after twenty-four hours. The early changes showed the cell protoplasm filled with large vacuoles, considerable swelling of the cells, and detritus in the lumen. After forty-eight hours the cells were more swollen, practically obliterating the lumen of the tubules and looking greatly like hypernephroma cells. Cell outlines were somewhat difficult to make out and the nuclei were frequently shrunken. Even ten days after a single injection the epithelium of the convoluted tubules showed marked changes. After fifteen days the epithelium was practically normal. In no animal was the phenolsulphonphthalein output reduced or the blood urea increased after a single injection.

These changes in the renal epithelium make it seem probable that repeated injections would have a marked effect, both on the histology of the cell and on renal function. From four to seven injections at intervals of from two to four days in a number of animals reduced the phenolsulphonphthalein output to as low

as 20 per cent, in one case even to 3 per cent, with a gradual return to normal even when the injections were continued. The changes in the tubules in these animals were much the same as after forty-eight hours in the experiments with a single injection. The kidneys were markedly enlarged, and the cortex swollen. Histologically the entire cortex gave the appearance of a hypernephroma in which the glomeruli stood out prominently from the light background of the clear cells of the convoluted tubules.

In order to control the histology of the kidneys more completely, in later experiments the left kidney was removed before the injections were started. In two animals the injections were given at intervals of a week for a period of about three months. In the first animal, changes in the right kidney were definitely different from those in the experiments in which the injections were fewer in number. The kidney was not so large; the cortex about normal in thickness, and on histologic examination cells, stained deeply with eosin, showed largely pink staining granules and rather deeply stained nuclei. There was definite proliferation of cells, so that in some areas there were two rows of cells lining the lumen. In many areas cells in various stages of degeneration could be seen. In the other animal, the kidney showed hypernephroma-like changes in the epithelium, the outstanding features being necrosis of the epithelium, numerous casts, and increased rows of cells lining the tubules. In spite of the fact that these animals had only one kidney the phenolsulphonphthalein output was 70 per cent and the blood urea was normal.

One striking and unexpected feature was the frequency with which pyuria developed in animals that had had three or more injections. In a series of thirty-six animals, fourteen developed pyuria which at necropsy was found to be due to an inflammatory reaction limited to the pelvis and peripelvic tissues. In no instance was the renal substance involved, and the inflammation was more markedly limited to the pelvic lining than in any experiments that I have made. In five control rabbits a positive culture was made from the urine, and in seven rabbits there was pyuria without, however, any renal changes observed at necropsy.

Recently, I had a patient with idiopathic streptococcal meningitis. In spite of lumbar drainage he showed an unfavorable course and was in a state of coma. It seemed probable that pressure was a factor in his condition, so an attempt was made to lower intracranial pressure by the intravenous injection of a 20 per cent solution of sucrose. Profuse diuresis was produced without, however, affecting the coma. He lived for forty-eight hours after the injection. At necropsy the kidneys were grossly somewhat swollen but otherwise showed nothing unusual. Microscopic examination, however, showed marked changes in all the convoluted tubules. The cells were so swollen that the lumen was reduced to a narrow slit or was completely obliterated. The protoplasm of the cells was granular and vacuolated. Numerous cells appeared to have no nuclei. No inflammatory products were noted.

Summary.—Repeated injections of a hypertonic solution of sucrose produces changes in all the convoluted tubules. The characteristic feature of the cells is their clear hypernephroma-like appearance. As many as thirteen injections have not produced a decreased phenolsulphonphthalein output or an increase in blood urea in spite of marked degenerative changes in the tubules.

THE DIFFERENTIAL DIAGNOSIS AND PROGNOSIS IN VARIOUS CLINICAL TYPES OF NEPHRITIS IN CHILDREN. DR. C. ANDERSON ALDRICH.

This paper summarizes points of importance in the prognosis and differential diagnosis of 186 children studied during the past ten years on the nephritic service at the Children's Memorial Hospital.

In estimating the prognosis, the differential diagnosis becomes of great importance because of the different outlook found in the different types of disease. Because it is felt that the usual method of anatomic classification in nephritis does not lead to accurate clinical diagnoses, and because this does not necessarily imply anything

as to the nature of the disease from which the patient is suffering, a method of classification based solely on clinical observations is recommended. The classification of these 186 cases and the diagnostic criteria are as follows:

1. Acute postinfectious hemorrhagic nephritis (120 cases):
   (*a*) Antecedent or concomitant acute, febrile infection
   (*b*) Hematuria
   (*c*) Benign course or death in acute illness
2. Chronic nonspecific nephritis (24 cases):
   (*a*) Edema
   (*b*) Hematuria
   (*c*) Hypertension
   (*d*) Increase in nonprotein nitrogen of the blood
   (*e*) Chronic course of death
3. Nephrosis (20 cases):
   (*a*) Marked edema
   (*b*) Absence of hematuria at all times
   (*c*) Normal blood pressure
   (*d*) Normal nonprotein nitrogen content of the blood
   (*e*) Marked albuminuria
4. Subacute bacterial endocarditis with nephritis (5 cases):
   (*a*) Edema
   (*b*) Signs of subacute bacterial endocarditis
   (*c*) Albumin, casts, red and white blood cells in the urine
5. Syphilis with nephritis (3 cases):
   (*a*) Criteria for diagnosis of chronic nonspecific nephritis
   (*b*) Diagnosis of syphilis
6. Tuberculosis with nephritis (2 cases):
   (*a*) Criteria for diagnosis of chronic nonspecific nephritis
   (*b*) Diagnosis of miliary tuberculosis
7. Renal infantilism (3 cases):
   (*a*) Criteria for diagnosis of chronic nonspecific nephritis
   (*b*) Physical infantilism

This method has the following advantages: 1. It can be applied accurately to each patient after proper observation. 2. Its use does not necessitate making exceptions in any large number of instances. 3. It implies something as to the nature of the disease from which the patient suffers. 4. It is not based on assumed anatomic lesions which seldom can be checked. 5. It indicates with a fair degree of accuracy the ultimate prognosis in each group.

Of the patients with acute postinfectious hemorrhagic nephritis 6.2 per cent died, the deaths being due to the infection that caused the nephritis, to cerebral complications or to anuria.

Of the group with chronic nonspecific nephritis 54.2 per cent died and none had entirely recovered when last observed. It is possible, however, that some of those who seem to be improving will eventually get well.

Of the patients with nephrosis 35 per cent died, 40 per cent recovered and 25 per cent showed urinary abnormalities when last observed.

Recovery was not noted in any patient of the last four groups.

Various practical points in the clinical observations and laboratory results are mentioned as they apply to the differential diagnosis and prognosis.

DISCUSSION

DR. BELA SCHICK: I think that one has to be absolutely sure, especially in the beginning, about the pathologic changes. In a study made several years before this meeting, a good prognosis of specific infection nephritis was confirmed in a case of nephritis following scarlet fever. One is surprised how many cases clear up. It is not known exactly what those patients will show in later life.

On my service at Mount Sinai Hospital, Dr. H. Schwarz and Dr. J. L. Kohn have studied thirty-eight cases of nephrosis in the last twelve years. Thirteen of the patients were lost track of; of the remaining twenty-five, sixteen died, six improved, and three were apparently cured. Dr. Schwarz and Dr. Kohn think that it is not safe to make a diagnosis of nephrosis until after at least six months of observation. All five of the patients who were examined post mortem, showed few changes in the kidney. There was some hyalinization of the glomeruli, but it was not comparable to that found in a real chronic glomerular nephritis. Of the patients who came to necropsy, we observed one for four years and another for three years; one had peritonitis four times and the other one three times. Perhaps the repeated attacks of peritonitis accounted for the changes in the kidney.

During the course of the nephrosis we observed interesting skin lesions, also the relative frequency of positive blood cultures of pneumococcus type IV, especially when the patient had temperature and chills.

Two cases were interesting in that the nephrosis cleared up after measles.

I think that Dr. Aldrich observed two cases of nephrosis in which improvement occurred after measles. Improvement in cases of nephrosis after other infectious diseases is also known.

DR. ALDRICH: I do not think that there is much to add, except that I have had the same experience as Dr. Schick. Patients with nephrosis should not be exposed to infectious disease, because they react poorly to infections; if they happen to get a fever, however, it is interesting to see whether the nephrosis clears up. We had five patients who recovered completely following acute septic infections. At the present time, I am considering malarial treatment for one of them in the hope that a cure will follow the fever.

In regard to the long period of observation in nephrosis—six months before the condition is called nephrosis—I do not see why a child cannot have a mild nephrosis as well as a severe type, one that clears up in a few months and one that does not clear up for twelve months. However, one is always uncertain in the diagnosis unless the condition has progressed for a long period.

In regard to the effect of acute postinfection hemorrhagic nephritis on the kidney, I observed at autopsy the kidney of a child who died of what was diagnosed as status lymphaticus four days after the first negative test of the urine following this type of nephritis. No gross pathologic lesion was found in the kidney. Microscopically, after a long search a few sclerosed glomeruli were found. On the other hand, in some instances marked changes are found in cases that are clinically indistinguishable.

PERSISTENT PYURIA AND ABNORMALITIES OF THE URINARY TRACT. DR. HOWARD REID CRAIG.

The pressing need for a closer and a more enthusiastic and understanding cooperation between the pediatrician, the urologist and the roentgenologist has prompted me to present a few cases from the pyuria clinic with which I am connected. I have purposely omitted from this report cases of transient pyuria, whether of the suppurative nephritic type or of the type that is secondary to other obvious foci of infection. When pyuria persists more than three or four weeks or recurs again and again over a period of months or years, it is time that a thorough investigation be made. We have made it a custom to use urinary antiseptics or alkalis during the early period of pyuria. With continued pyuria however, in addition to a detailed history and physical examination, a flat roentgenogram of the abdomen and a cystogram are necessary. The latter will often yield startling results. The presence of residual urine in the bladder should be determined. The blood nitrogen, phenolsulphonphthalein output and blood pressure should be estimated and finally, carefully taken cultures should be made on suitable mediums from the urine, stool, tonsils, retropharynx or other accessible foci. At this point the need for cystoscopic examination often suggests itself. Clear visualization of the bladder and its orifices, determination of the urinary

urea and dye excretions to compare the function of the two kidneys, catheterization of the ureters with culture and examination of the urine and finally pyelography have proved of inestimable value in demonstrating many of the underlying factors producing chronic pyuria.

We report twelve cases demonstrating: (1) compression of the ureter from without (*a*) by a mesenteric cyst and (*b*) by embryonal adenosarcoma of the kidney, (2) neuromuscular dysfunction with atonic bladder, (3) stone in the left ureter, (4) diverticulum of the bladder, (5) spasm of the ureter and bladder, (6) double pelvis and ureters, (7) bulging bladder floor, (8) aberrant blood vessels, (9) angulation from ureter nephroptosis, (10) malformation of the perineum, (11) ureteral strictures and (12) two instances of dilated ureters of undetermined cause.

Emphasis should be placed on the need for complete medical and urologic investigation in every case of pyuria that persists for more than four weeks. Abnormalities of the urinary tract may persist for years without infection but once it occurs, the pyuria becomes persistent. Abnormalities of the urinary tract are much more frequent than is generally recognized by pediatricians. Our experience has taught us that, after the first four weeks of pyuria, early investigation medically and urologically will save irreparable and often fatal damage to kidney tissue and function later on.

DISCUSSION

Dr. Richard M. Smith: There are two or three things worth emphasizing in connection with children with pyuria. The former conception of pyelitis is changing somewhat. Pyelitis or pyuria was considered as a disease confined almost entirely to female infants.

The condition in males is almost always associated with congenital phenomena of the urinary tract. It seems to me, therefore, that it is important to emphasize more than we have the sex of the patient.

Chronic pyuria in the male patient is almost invariably associated with a congenital abnormality. This is particularly true in young male infants. It has been my experience that there is a lesion in those instances, sometimes single, but usually double.

Another thing that is important to emphasize is the value of cystograms.

An important element of the technic is to exert some pressure in introducing the iodide. In several instances I have observed that the first plate showed no abnormality, but that after a little more of the solution was introduced, the reflux into the ureter was clear and an abnormality was demonstrated.

In females who have a persistent pyuria, there is a possibility of congenital phenomena also, but in males they occur in all cases; simple pyuria is limited almost entirely to females.

Dr. Ella Schick: I should like to call attention to the fact which Dr. Smith brought out, that is, the new method of intravenous injection which I think is important for the pediatrician. It is a method of injecting uroselectan (an iodopyridine compound). Recent results with this method are excellent. It has been found very useful in male children, because of the difficulty of cystoscopy. I think that it is the method of the future. The pictures are very clear, and I think it will soon be possible to use this preparation in general practice.

Dr. Henry F. Helmholz: I should like to emphasize one point that Dr. Craig made, namely, that infection is of importance in cases that show malformations. When it is realized that about 5 per cent of all infants have malformations, it is only a relatively small percentage of this group that has infections; when an infection is acquired, however, it probably remains until the abnormality has been corrected by surgical measures or until the patient dies.

I want to emphasize that certain of these chronic infections, even when they have lasted from six months to six years, can be cleared up by intensive drug therapy. We have had a series of about twenty cases in which the infection has lasted for many months that we have been able to clear up by intensive hexa-

methylenamine therapy. We have found uroselectan a valuable adjunct in the diagnosis of diseases of the urinary tract in childhood.

Our experience with infections in boys does not bear out entirely what Dr. Smith has said. We have seen a considerable number of infections in boys, particularly within the first week of life, that have cleared up. We feel therefore that there probably was no abnormality of the urinary tract. It must be assumed that the coli bacilli not infrequently gain entrance to the blood stream during the first few weeks of life.

Dr. Richard M. Smith: The observation mentioned is true of the new-born. The phenomenon is quite different from what it is later.

Dr. Joseph Brennemann: It seems surprising it has taken so long to find out the truth of what Dr. Craig has said about the frequency of urinary anomalies. In a series of 176 autopsies, there were 13 major anomalies of the urinary tract. I think that some of the points made should perhaps be checked up pediatrically and chronologically.

Years ago pyelitis was often seen in female children, as observed by Dr. Smith. Practically, without exception, they recovered after a time. Many of them had repeated infections. In many cases the condition lasted for a long time. There is a certain advantage in seeing some of one's medical grandchildren. The first case of pyelitis that I ever encountered I saw several times through several attacks about twenty-five years ago. Dr. Abt, who later had the case, diagnosed it as pyelitis. I have since taken care of that patient's children. She has gone through several pregnancies and has never had a recurrence of pyelitis. She is well in every way.

I am perfectly in accord with the idea that if the pyuria does not clear up after a certain length of time the urologist should be called in. I rather object to saying that this should be done at the end of four weeks, as I do not like to be so specific ordinarily in medicine. There are times when I am willing to treat a child for a long time before I have a urologic examination made, but the urologist is always ultimately called on if the condition does not clear up.

My experience has been practically the same as Dr. Craig's, except that I do not think I have found so many causes of urinary obstruction. One type, of which I have seen several examples, was not emphasized as much as I would emphasize it.

Dr. Craig spoke of a "narrowing of the urethral opening." I would not describe it that way in the cases that I have seen. In those cases there was not a narrowing of the urethral opening, but an obstruction to the outlet without an obstruction to the inlet. Although one could easily insert a catheter, the patient had an obstruction at the neck of the bladder caused by a valvelike formation that produced incomplete obstruction; this made the bladder and both ureters enormously dilated.

Dr. Craig: There are one or two points on which I want to comment. In connection with the statement that Dr. Helmholz made about hexamethylenamine, we use it, but we continue our investigation just the same.

We have not yet used uroselectan, but are about to do so.

In regard to sex, in this very small series of twelve cases there was one male patient who had multiple stricture of the ureter.

In connection with the time at which the urologist should be called in, I think that sometimes he should not be called in at all. In a great many of these cases it is the cystogram that tells a good part of the story. It takes an understanding urologist to carry on the work. The urologic work here has been done by Dr. Campbell, who has been enthusiastic and efficient.

The Composition of Growth. Dr. William W. Swanson.

The composition of growth in infancy in this study was limited to determinations of the retentions of various minerals and nitrogen per kilogram of gain in weight. Hamilton (Hamilton, B., and Moriarity, M.: The Composition of

growth in infancy, Am. J. Dis. Child. **37**:1169 [June] 1929) showed that the comparison of a kilogram of gain in weight in a premature infant as compared with the body composition of the infants born at full term presents interesting variations. It should be stated here that this study was undertaken at his suggestion. The object of this study was to determine and compare the composition of growth in infants fed on breast milk and cow's milk over a long period; further, to obtain more data on the retention of sodium, potassium, chlorine and magnesium within the normal range than are at present available in the literature.

The experiments were carried out on two normal full-term infants. One was placed on a mixed breast milk and the other on a powdered cow's milk feeding. Retentions were then studied over a period of four months in the two infants. The preparation of feedings, the collection of specimens and the analyses of food and specimens will be given in detail in a later paper.

The retentions obtained for growth in the two infants show several interesting facts. The amounts of nitrogen, potassium, sodium, chlorine and magnesium per kilogram of gain in weight are much higher than the values found per kilogram of body substance at birth (Camerer, Soldner: *Ztschr. f. Biol.* **39**:173, 1900; **40**:559, 1900; **43**:1, 1902). The amounts of calcium and phosphorus per kilogram of growth falls far below the value for these minerals per kilogram of the body composition at birth, and the data corroborate the observations of Hamilton in a similar study of the premature infant. The low calcium and phosphorus retention in early postnatal growth is apparently a normal condition and probably indicates that the infant during this period is supplied with these minerals from storage somewhere in the body. Dr. E. A. Park has pointed out that the cortex of the long bones is thicker at birth than later in infancy and evidently serves as a source of calcium and phosphorus supply during the period of early growth.

The data obtained, further, show that 1 Kg. of growth contained much more minerals and nitrogen in the powdered milk fed infant than in the breast fed infant. This difference cannot be accounted for by differences in either adipose fat or interstitial fluids. Boldt and his co-workers (Boldt, F.; Brahm, C., and Andresen, G.: *Arch. f. Kinderh.* **87**:277, 1929) advanced the idea that this hypermineralization is only temporary and is due possibly to storage, and that at some favorable moment the cow's milk fed infant has a period of demineralization. Such demineralization did not take place in the infant fed on powdered milk during the five months' period of observation. This study, therefore, indicates that the most distinctive difference found in the two infants fed on breast and cow's milk was a marked difference in the amounts of minerals and nitrogen entering into the composition of growth.

Dr. Bengt K. Hamilton: A study of the composition of growth is an elaborate undertaking. It has taken Dr. Swanson a year to collect his data. That is probably the reason why, though there are all kinds of information about variations in the quantity of growth, practically nothing is known about the variations in the quality of growth, as Dr. Swanson has shown. Because two infants grow just about the same amount, it is not a certainty that growth in respect to the composition is the same. Of course, breast-fed and bottle-fed infants react differently in many respects. One kind of infant is more susceptible to all kinds of disease than the other. I think that the type of work that Dr. Swanson has been doing might possibly yield some more exact information as to what causes this difference.

A Statistical Comparison of Weight, Growth and Morbidity During the First Year in Breast-Fed and Bottle-Fed Infants. Dr. Harold K. Faber and Dr. T. Leonard Sutton (by invitation).

The paper will be published in a later issue.

DISCUSSION

DR. CHARLES HERRMANN: In making a comparison of this kind, I think that it is important to know whether the babies were weaned because the mother, who had successfully nursed other babies, had to go out to work, or whether she weaned the baby because she had no breast milk. I think that it would be a good plan to separate the groups and not consider them at all under the heading of those artificially fed.

I think that the only way superior immunity can be proved conclusively is in the study of a series of identical twins, one of whom is breast fed and the other bottle fed.

DR. ISAAC A. ABT: Will Dr. Faber inform us concerning developmental conditions? Did the breast-fed children erupt their teeth earlier; did they learn to sit, talk, and walk earlier?

Perhaps, after all, mere increase in weight is not an absolute criterion of progress. Possibly a breast-fed infant is healthier than a hand-fed infant that gains more.

DR. FRANKLIN PAUL GENGENBACH: Since the decrease in morbidity and mortality in bottle-fed infants has been largely due to the improved hygienic handling of the milk, was the milk that the babies received raw, pasteurized or boiled? I always ask the mothers to heat the milk for ten minutes in a double boiler.

DR. JOSEPH BRENNEMANN: I think that this paper is interesting, especially the last part, which is somewhat surprising; however, a phase of that problem has to be seriously considered. What is a breast-fed infant? I have tried for a good many years, in considering statistics of this sort, to decide what constitutes a breast-fed infant. Is an infant that nurses for two months, or one that receives only one or two feedings a day for ten months a breast-fed or a bottle-fed infant?

In the second place, the statistics would be valuable if Dr. Faber had fed every one of those babies himself as one feeds a baby in private practice when one keeps in close touch with the case. For instance, there is the question of when to wean a baby. I do not recall ever having weaned a baby. One wants to be sure that a baby has enough nourishment.

In certain infant welfare societies, one of which I know especially, mothers are taught not to give artificial foods as long as the baby is progressing reasonably well on the breast. To my mind, that is pernicious teaching. If one has the idea that a baby ought to be kept on the breast, which is very commonly done, for too long a time, or that it is not given enough other food, one might easily get such results as those reported. I think that the results given in the first part of the paper depend entirely on what was done for every baby, before one is justified in making deductions as to whether breast milk or cow's milk is of greater relative value.

The question is extremely interesting, but I do not think that one should question the value of mother's milk.

DR. FABER: I do not question the value of mother's milk. I question the present information as to the normal average weaning time. I do not believe that there is anything sacred about the weaning time. It is different in all mammals. Many of them start to eat other food than milk within a day or two after birth. The actual period of complete weaning is extremely variable between species.

All the babies of the breast-fed group received enough breast milk to maintain them in fair nutrition, at least, for a period of six months or longer. I take that as being a fairly good test of an adequate supply for the cases studied.

I have checked up on a good many of my private cases and have found that at present the average mother does not continue to have sufficient breast milk to give her baby the supply needed for much over three months. I think that this is a fairly common experience. One can bully the mother into putting the baby to the breast for a longer time but one cannot often make her have more milk.

Dr. Abt asked about the developmental history of these infants. I do not know; I have no data. I am reminded of a paper that appeared recently which showed that breast-fed babies developed mentally much better and reached a higher degree of intelligence than bottle-fed babies. That seemed to me rather doubtful in itself. I went over the report of Professor Terman to see what proportion of his extraordinarily bright children had been bottle-fed and breast-fed. About 40 per cent of them had been bottle-fed. I do not believe, therefore, that any serious harm has been done to the intelligence of babies through bottle feeding.

Dr. Feingenbaum asked how the milk was treated. Most of it was pasteurized. Our clinic mothers, as a rule, cannot afford certified milk. In any case, it has been our practice, with some exceptions, to have the milk boiled, at least for the first few months of life.

MALNUTRITION IN INFANCY DUE TO CHRONIC INFECTION. DR. HENRY HEIMAN and DR. PHILIP COHEN.

Although chronic infection had previously been assigned as an etiology for marasmus, nevertheless our impression from reading the literature on this subject is that the disorder is usually caused by a constitutional metabolic aberration or by a series of improper feedings. Our observations on a series of cases recently seen point to the conclusion that with the exception of congenital anomalies and poor feeding, which form a minority of these cases, the metabolic abnormalities are due to chronic infection. That such an effect can be due to tuberculosis or syphilis is well known, but there are other infections, not so obvious or so easily diagnosticated by roentgen studies or laboratory data, that can and do produce the same metabolic result.

The cardinal clinical sign of marasmus is the progressive loss of tissue; the characteristic chemical manifestations of marasmus are loss of water, nitrogen and salts. The other chemical phenomena, the relative acidosis, the increased excretion of organic acids, the increased ammonia coefficient of the urine, etc., can occur in other conditions. It is more than a coincidence that the same symptoms and chemical manifestations are present in infections. In addition, the fever in infection raises the basal metabolism. The most recent metabolic studies in marasmus, as a fixed state, reveal little true abnormality beyond what is already known of chemical changes.

It is our belief that in modern pediatrics infection is by far the most important single factor in the evolution of marasmus. We found that when the infection was cured or alleviated, the loss of tissue ceased and a positive nutritional balance was attained. In this respect, the relation of infection to marasmus bids fair to equal the rôle it plays in the causation of alimentary intoxication, an observation that has justly received much emphasis in the last few years.

DISCUSSION

DR. ALFRED HAND: Dr. Heiman's paper recalls several illustrative cases that I have seen. An infant, aged about 15 months, had marked emaciation, irregular fever and moderate leukocytosis; in spite of repeated examinations no focus of infection could be found. I tried to persuade the otologist to open the mastoids although the roentgenograms were negative. Autopsy showed what had not been suspected in the absence of any suggestive symptoms: empyema of the gallbladder. In a second case, an infant, aged 7 months, in whom feeding was difficult, showed consolidation of the base of the right lung, with a febrile course for a few days; then the temperature was normal for some time and the Mantoux test was negative, but all lines of feeding that were tried failed to bring improvement. Autopsy showed tuberculous consolidation of the lower lobe of the right lung.

Even when the focus of infection is found and removed, recovery does not always follow as in a longstanding case of empyema that I reported to the

society several years ago. It had probably existed for twenty-one months, and the patient's appearance was distressing. The aspirating needle could be felt to grate through a very thick pleura, and greenish pus was evacuated; drainage was instituted, but the disturbance of nutrition was too profound for recovery.

DR. HEIMAN: I have nothing to add, except to say to Dr. Hand that he need have no regret in not having diagnosed suppurative cholecystitis in an infant.

Third Session

Evening, June 17

HYPERPYREXIA OF ONE YEAR'S DURATION, OF UNKNOWN ETIOLOGY. DR. J. B. BILDERBACK.

A boy, aged 6½ years, had had an almost continuous elevation of temperature since the age of 4. Previous to this illness he had appeared healthy. The family and past history were unimportant. After having a high fever for one month, associated with marked abdominal pain, the child was admitted to the hospital where he remained for 184 days during which time he ran an irregular septic temperature. Sometimes the temperature reached 107.6 F.; generally it ranged between 103 and 106 F. Usually there was a daily rise. The physical examination yielded practically negative results. During his stay in the hospital nearly every known test was made and repeatedly checked in order to make a diagnosis. After six months of hospitalization the patient was discharged with a persisting fever.

He was under observation while at home and was readmitted to the hospital several times for further investigation, but a definite diagnosis was not made. He was carefully studied for tuberculosis, malaria, sinus infection, undulant fever, syphilis, Hodgkin's disease and infection of the urinary tract. The observations were all negative. On two occasions during the year he complained of pain in the knee and wrist associated with a generalized hypersensitiveness. The pain in the joints was so transitory, lasting but a few hours, and the pain in the abdomen so marked that a diagnosis of beginning arthritis did not seem reasonable. After eighteen months of almost continuous fever, however, marked with wide fluctuations, sometimes with a variation of 9 degrees in twelve hours, the patient began to show unmistakable evidence of chronic infectious arthritis. As a rule, chronic arthritis attacks the small joints first and the temperature is not so high or so widely fluctuating. At the present time the case is typical.

DISCUSSION

DR. JOSEPH BRENNEMANN: At one time, I saw a case similar to the one reported. A child, aged 11 months, had a daily temperature of from 103 to 105 F. I could not find anything to account for the temperature. At times he had a little arthritic pain, and occasionally a little swelling. He was taken into the country, and several months later I heard that he was well.

DR. ISAAC A. ABT: This interesting paper should not pass without a word of favorable comment. Clinical reports of this kind, carefully prepared and excellently presented, should awaken general interest.

The course of this disease suggests a sepsis lenta. Sometimes such an infection eventuates in a cardiac lesion, subacute bacterial endocarditis or in rheumatoid arthritis.

The spesis lenta, with its rheumatoid complications, is not unlike tuberculosis. Whatever the causative organism is, rheumatoid arthritis resembles in many ways a tuberculous infection. Tuberculosis attacks the lungs, bones, joints and other tissues, but rheumatoid arthritis, or the kind of sepsis that Dr. Bilderback has referred to, selects principally bones and synovial membranes, enlarges the spleen and is accompanied by anemia and a septic temperature.

DR. ALFRED HAND: Although the blood cultures have been negative, I feel like making a snap diagnosis of a hemolytic streptococcic septicemia because of the striking resemblance of the chart to one that I have, which, however, ran for only fourteen weeks. In my case positive blood cultures were obtained repeatedly. A point of resemblance is in the development of localized edema which shifted from one region to another, the patient finally overcoming the infection.

In another instance of fever of long duration, there were distinct localization: first, pneumonia of the apex of the right lung, then of the apex of the left lung, followed immediately by erysipelas which made the tour of the body several times, the combined courses lasting for two and a half months.

From the clinical standpoint it would seem that DR. Bilderback's patient is infected with streptococci of low vitality, so few occurring in the blood stream as to escape detection.

DR. BENJAMIN KRAMER: I shall place on record a case that in many respects is similar to the one reported by Dr. Bilderback.

E. J., a boy, aged 3 years, had as the chief complaint fever of five weeks' duration. The family and previous history was unimportant.

The temperature varied between 101 and 105 F. There was stiffness of the neck for a few days. Physical examination yielded negative results except for palpable superficial lymph nodes, large, ragged tonsils and a palpable spleen.

The urine was normal. Examination of the blood showed: hemoglobin, from 60 to 70 per cent; red blood cells, from 3,600,000 to 4,200,000; white blood cells, from 8,400 to 9,800; polymorphonuclears, from 39 to 59 per cent; lymphocytes, from 49 to 50 per cent; eosinophils, from 4 to 7 per cent, and platelets, 270,000. The Wassermann and Kahn reactions of the blood were negative. A culture from the nose and throat was negative for Krebs-Löffler bacilli. The tuberculin (intradermal) test with 5 mg. was negative. The Dick test was negative. The Widal test was negative for typhoid and paratyphoid A and B bacilli. The agglutination test for dysentery was negative (Dreyer technic). Cultures of the blood were sterile. The spinal fluid was normal. The agglutination test for *Bacillus melitensis* and *Bacillus abortus* was negative. Roentgenograms of the chest, extremities and sinuses were negative. Examination of the stools revealed no ova or parasites. The diagnosis was fever (unexplained) and the patient was discharged from the hospital. On Dec. 30, 1929, he was readmitted with the complaint of fever of five months' duration. Three weeks before, the joints and lymph nodes had become swollen.

Physical examination revealed an undernourished, fretful child with symmetrical swellings of the wrists, knees, elbows and ankles. There was no redness. An excessive growth of hair was seen on the back and the exterior surfaces of the extremities. All the superficial lymph nodes, including the epitrochlears, were markedly enlarged. The spleen was no longer palpable. The swellings about the joints were not hot or tender. Cultures of the blood and fluid aspirated from the joints were reported by Dr. Kerley to be sterile. The diagnosis of Still's disease was made.

A tonsillectomy was performed in April, 1930. The fever gradually subsided. The patient was reexamined on June 25, 1930. Two weeks before, the symptoms had recurred; the temperature had reached 103 F., and the wrists, elbows and ankles had become swollen and painful. The patient weighed 28 pounds and 6 ounces (12.8 Kg.). The temperature was 100 F. The spleen was just palpable, the superficial lymph nodes were enlarged, and there was some contracture of the left hip.

This patient furnished a diagnostic problem for four months, presenting the syndrome of unexplained fever, with a palpable spleen and enlarged lymph nodes. The history of stiff neck of several days' duration gave a clue to the nature of the condition which was apparent when the swellings appeared in the joints.

DR. BILDERBACK: My patient has recently been readmitted to the Children's Hospital. He still has a fever, and his general condition remains the same.

Undoubtedly he has a pyogenic infection, probably streptococcal. The remarkable thing about the case is that the infection persists so long without definite localization.

OBSERVATIONS ON THE THYMUS GLAND. DR. WALTER LESTER CARR.

Roentgen examinations of new-born infants at the Woman's Hospital showed a transverse thymic shadow on the lower border of the third dorsal vertebra; in one group it measured 2.7 cm. and in another, 3.1 cm. Two infants had measurements of 4.5 and 4.6 cm. No especially large thymus was discovered. The records of the New York Eye and Ear Infirmary in 31,163 operations showed three deaths in children between 5 and 9 years of age from what was regarded as a thymic cause. The Medical Examiner's Office reported the deaths of sixteen children under 10 years of age in whom the thymus was examined. In five cases the average weight of the thymus was a little over 31 Gm.; the average weight of the thymus in children not operated on was 29.6 Gm. The Department of Health reported eighty-two deaths (0.733 per cent) from thymic disease in children under 10 years of age.

It must be decided whether roentgenograms made at the time of birth show anything of value compared with the plates made in later childhood. In the latter group it is essential that a physical study should be made of a child before operation. A roentgen record adds to a more thorough knowledge of a patient and is also a safeguard against the criticism of neglect. Anesthesia properly administered by a competent anesthetist minimizes the danger from what is designated as thymic death.

DISCUSSION

DR. OSCAR M. SCHLOSS: It is difficult to determine what symptoms are due to the thymus gland. There is no evidence that the gland furnishes an internal secretion, and its removal gives rise to no recognizable symptoms. Doubtless much of the present confusion has arisen from the fact that roentgenograms show a considerable upper mediastinal shadow in normal infants; consequently the diagnosis of thymic enlargement is often erroneously made. Certain patients presenting the general characteristics of status thymicolymphaticus often die from trivial causes, but proof is entirely lacking that such deaths are regularly due to the thymus gland. It is possible, as Marine has suggested, that the real fault in such cases is suprarenal deficiency, a view that is supported somewhat by the observations of McLean and Sullivan.

The thymus gland wastes rapidly in all acute diseases. In cases of sudden death it is possible that the thymus is large because it has not wasted. This view has as much in its favor as the supposition that the sudden death is due to thymic enlargement. I say this with the knowledge that a few cases have been described in which there was evidence that the thymus exerted pressure on the trachea; such cases are very few and furnish no proof that this is the usual mechanism of death.

The sudden deaths during anesthesia or minor operations are not characteristic of asphyxia produced by pressure on the trachea or bronchi. The symptoms are more suggestive of sudden circulatory failure.

There is evidence that the size of the thymus is related to nutrition, as pointed out by Boyd. Postmortem examination of an emaciated infant never discloses a large or even a normal thymus gland. Similarly, in roentgenograms one sees a large upper mediastinal shadow only in well nourished infants.

Observations on three infants in our clinic furnish additional evidence in favor of this view. On admission these infants were suffering from acute infections, were well nourished and showed large upper mediastinal shadows on roentgen examination. With the occurrence of emaciation, the size of the upper mediastinal shadow diminished markedly, but increased again during convalescence when the normal weight was regained.

The discovery of a large upper mediastinal shadow in roentgenograms of the chest of newly born infants is responsible for attributing to the thymus many varied symptoms that may occur during the first two weeks of life. Such symptoms as convulsions, cyanosis, crowing, noisy or rapid breathing, etc., are frequently due to cerebral hemorrhage, pulmonary inflammation, congenital laryngeal stenosis and other causes. The discovery of a large upper mediastinal shadow in a newly born infant is no evidence that the symptoms are of thymic origin, for such shadows are frequently present in normal infants. Moreover, the disappearance of these symptoms after three or more roentgen treatments at intervals of from ten days to three weeks is not a convincing therapeutic test, for such symptoms frequently disappear spontaneously in this length of time.

On the other hand, there is no doubt that an enlarged thymus gland can and does cause symptoms by pressure on the trachea or bronchi. It is my belief, however, that such cases are not frequent. Their diagnosis should rest on something more than a broad upper mediastinal shadow. The technic of taking lateral roentgenograms of the chest, as developed by Pancoast and Prendergass, which show the thymus and trachea may offer a definite means of diagnosis.

Dr. J. P. Crozer Griffith: I can merely corroborate what Dr. Schloss has said. I believe thoroughly that there is such a thing as thymus death, if one wants to call it by that name; that is to say, a sudden death often associated with the presence of a large thymus gland. Many years before this meeting, I saw a family in which eight children had died suddenly in infancy. I had been called in consultation to see the ninth baby, who was, at that time, apparently perfectly healthy; however, he died and an enlarged thymus gland was found at autopsy. Several years ago, a woman brought her baby to the hospital. She described it, in her broken English, as dying every day. It did suddenly die while in the hospital, and autopsy showed an enlarged thymus. Now this, while suggestive, does not actually prove anything whatever, certainly not that the enlargement of the thymus was the cause of the sudden death. Clearly, there is a condition that renders children liable to sudden death from slight causes. One may call it status lymphaticus or thymus death, but to my mind the thymus itself is in no way the factor. It is only an anatomic manifestation of the constitutional condition, a result but not a cause.

Of course, I am leaving completely out of consideration the rare but indisputable cases in which death has resulted from thymic pressure on the trachea. This is an entirely different condition, regarding which there can be no dispute. We are discussing the sudden death of children who have not shown the characteristic symptoms of this condition. Children who die of thymic pressure have generally exhibited symptoms of stenosis for some time. That, as stated, is not what we are talking about. The reasoning of some medical writers seems to be somewhat as follows: There is a certain series of symptoms produced by enlargement of the thymus gland. If the child is given roentgen treatment these symptoms disappear. Therefore, the thymus gland produced the symptoms. This method of reasoning does not seem to me to be good logic. For many years this so-called thymus death has interested me greatly, and I have written about it at times. As far as I have discovered from my own experience or from consultation of the literature, however, there is no set of symptoms except continued stenosis of the trachea that can properly be attributed directly to enlargement of the thymus gland. It is an assumption without any actual proof and, consequently, it seems to be imperfect logic to maintain that because any of these symptoms are observed the thymus is responsible. It is not really known how large a thymus may be within normal limits. It is not even known, as yet, that the present methods of examination can show definitely when thymic enlargement is present. Roentgenologic methods do not seem to disclose with certainty whether a shadow in the thymic region is provided by the thymus or by something else. Moreover, it has been proved many times by autopsy that thymic enlargement is not certainly

associated with sudden death. There may be enlargement of the thymus, without sudden death, or sudden death with no noteworthy enlargement of the thymus. It therefore seems to me that the logic is wrong; conclusive pathologic and clinical proofs are lacking.

Not long ago some physicians published a report of about fifty cases showing symptoms that they attributed to the thymus. Roentgen treatment was given and recoveries amounted to about 96 per cent; I do not remember the exact figures. This again proves nothing. It must be demonstrated (1) that thymic enlargement was actually present and (2), if this was the case, that the symptoms were clearly dependent on this condition and (3) that the infant would not have recovered as completely if untreated. As to the therapeutic value of roentgen exposure of the thymus region in young infants, admitting for the sake of argument that it is of service, it still is not known whether the good results were from the action on the thymus or from the effect on some other structures. Regarding the need of such treatment, which I do not maintain is or is not effective, I can only say that young infants have been sent to the hospital repeatedly with a diagnosis of enlarged thymus already made, or perhaps made by the interns at the time of admission, and that the symptoms have shortly disappeared without roentgen treatment. Finally, roentgen therapy is a powerful agent capable of doing harm as well as good. I do not feel sure that treatment of the thymus region with roentgen rays is entirely without danger. I saw one case in consultation with Dr. Dannenberg in which we could attribute the fatal results to nothing but this treatment. Of course, I have no actual proof of this, but Dr. Dannenberg found a number of such cases reported in the literature.

Dr. DeWitt H. Sherman: It is important and difficult to evaluate the significance of an enlarged roentgen shadow in the thymic area of the chest.

One of my associates, Dr. Edward C. Koenig, of Buffalo, made roentgen examinations of the chests of 100 new-born infants and watched them for a month. He found about 15 per cent with an enlarged thymus shadow but only one of them had symptoms that could be attributed to an enlarged thymus.

Because there is a true thymus death, should every new-born infant be given roentgen therapy whether it has symptoms or not? I believe that it is safer to do so because (1) roentgen treatment seemingly does no harm and (2) it generally reduces the size of the thymus gland; if the size of the gland indicates the degree of the dysfunction, treatment should be given. Another reason for treatment is to relieve one of personal or professional responsibility. If treatment is given for the enlarged shadow and if the shadow decreases, everything possible has been done to protect the infant. Should anything vital then happen, the physician is free from censure.

Most of these shadows promptly decrease in size; if they do not, the condition appears to be not a physiologic increase in size and function but a pathologic hypertrophy of a questionable nature.

To the intellectual, conscientious, painstaking mother the question of the thymus gland has caused untold mental anguish. She knows of its abnormalities, has heard of sudden thymus death and must know of the size of the thymus in her offspring as shown by roentgenograms. I recently had an amusing experience. Twins were born in Canada, and roentgenograms were made as a routine measure. One infant had an enlarged thymus shadow and was given roentgen treatment. This infant was observed innumerable times each twenty-four hours to relieve the mother's anxiety as to whether it was still alive. I examined the roentgenograms, saw an enlarged shadow in one of them, but learned that the other twin had been treated with roentgen rays. Both twins thrived.

For such anxious mothers one must be charitably cautious in arousing unnecessary fears about their offspring. For years in Buffalo innumerable infants and children suffered from acidosis, a diagnosis made in every more or less obscure or recurring upset. Fortunately, this cause of maternal anxiety has been decidedly lessened. Then came the greater worry about the dangers of the thymus gland

I trust that the attitude of physicians toward this indefinite condition may also be rationally altered.

It is convenient for a practitioner to have acidosis, thymus, status lymphaticus or, as recently reported, alkalosis as the designated cause for a disaster. The sensitive, fearful, conscientious mother should be considered humanely, however, in making a diagnosis of any of these conditions.

Dr. Rowland G. Freeman: These cases of sudden death may not be due to thymus, but for 250 years the thymus has been associated with sudden death. In cases of sudden death in children one usually finds a very large thymus. I am willing to admit that the figures of Bovaird and Nichols at the Foundling Hospital probably gave the weight of the normal thymus too low. The children on whom they performed autopsy were all malnourished and naturally had a small thymus. I think that the normal thymus is probably larger than the size that they gave. There are certain symptoms that seem to be definitely associated with enlargement of the thymus. If physicians want to protect themselves, they must treat children who have those symptoms.

I believe that an infant who cries hard, holds its breath and becomes blue has some obstruction in its chest that is due to pressure on the blood vessels; this is usually due to a large thymus. Other symptoms are due to pressure on the nerves. These symptoms will disappear after proper roentgen treatment, I believe. One must therefore not disregard the thymus entirely, but appreciate the great danger to the child if it is enlarged and causes symptoms.

Adults with lymphatic conditions are very susceptible to certain diseases and to sudden death. In a series of cases at Bellevue Hospital, Dr. Emerson found that 50 per cent of the children with meningitis had large thymus glands. Whether improvement would result from treating the patient for early symptoms of enlarged thymus, I do not know, but it might do them much good, and I believe that it is worth thinking about. I would not be willing to withhold treatment from a child with marked thymic symptoms. Sometimes the results of treatment are dramatic; in other instances improvement is slow.

I saw one child, 2 months of age, who was having convulsions several times a day, and who was not sleeping more than fifteen minutes at night. It had attacks of choking, and apparently was about to die. One roentgen treatment relieved the child of all its symptoms. I think that any physician who has such a case cannot help but observe similar symptoms when they occur in other children.

Dr. Joseph Brennemann: I doubt whether there is any subject that one could bring up on which one would hear longer discussion and more divergent ideas.

I agree thoroughly with what Dr. Schloss has said with reference to the size of the thymus and its relation to the nutrition of the child. A physician who recently reviewed the last 1,000 autopsies at the hospital with which I am connected checked up on the weight of the thymus. In not one malnourished infant who died was the thymus larger than what is regarded as normal.

There is a practical aspect to this whole matter at the present time. Mothers now commonly do not ask whether they should have the child examined for a thymus. They have a roentgenogram made and then let the physician know the verdict.

I observed one child who had a large shadow. I told the mother that I did not know whether it was a thymus or not. The child had three roentgen treatments and the thymus became smaller. About three weeks later, the child was found dead in bed. There was, unfortunately, a strap across its neck at the time. When a case like that happens and is reported in the newspapers, all the mothers want their babies checked up with reference to the thymus. I was glad to find that in the case mentioned I had given the child three treatments.

I think that there are two different things associated with the thymus that are apt to be confused with one another. There is a thing that one might speak of

as hyperplasia of the thymus gland which occurs commonly in earliest infancy and which in a few instances, I am sure, causes symptoms of pressure. I have seen a number of cases in which there was a large shadow and stridor. The child was given roentgen therapy, and the shadow disappeared after treatment, as did the stridor.

On the other hand, when a child dies suddenly without evident cause and comes to autopsy, almost without exception one finds a pathologic complex that is not observed under ordinary circumstances. The child has a larger thymus than ordinary. The mesenteric and mediastinal lymphatic glands are greatly enlarged, and there are petechial hemorrhages. That condition is found too frequently to be ignored. It would take more than the authorities who have spoken tonight to make me believe that there is not something that might be called a thymus death. The term may be wrong, but there is a definite symptom complex that for want of a better name one might as well call thymus death.

The pendulum has swung back and forth, as it does in many medical controversies. One of our Canadian confrères wrote a paper several years ago pointing out seven symptoms due to the thymus. A roentgenologist in Philadelphia frequently reports compression of the trachea as a symptom due to the thymus. At the present time, the tendency is to say that there is nothing to the whole idea. I think that the pendulum is going to swing back to a medium position. In the meantime I shall continue to have all children with symptoms suggestive of thymic enlargement examined and treated roentgenologically.

Dr. Carr: I appreciate the comments of Dr. Schloss. Unquestionably the influence of disease makes a change in the thymus. The records of which I spoke seemed to be so diverse that I thought perhaps an interpretation might be made from the statistics reported.

The statement made by Dr. Brennemann in connection with enlargement was brought out when Dr. Pancoast of Philadelphia spoke at the Academy of Medicine on enlargement with pressure, making it a distinct condition of what is often spoken of as thymic death.

As has been stated, physicians vary in their point of view of what is thymic death. At the New York Eye and Ear Infirmary there were no autopsies, but the records show the mortality to be almost negative in tonsil and adenoid operations. There must be an influence from the method of anesthesia. In the operations in which death occurred, as reported in the paper, perhaps the anesthetic was administered by some one not particularly well equipped to do this type of work.

The first point that I want to make concerns the advisability of having a roentgenogram made of the thymus and the chest of the new-born infant as part of the records, which Dr. Brennemann referred to as often being desired. Whether such a record will be of value as part of the history of an infant must be determined by the physician and the hospital.

The next question is: Can one determine before operation whether a roentgenogram of the thymus is going to be of assistance, and whether treatment by roentgen therapy would be of benefit if there is an enlargement of a distinct thymic shadow that is not mediastinal or indicative of a change in the lung or heart?

One of the cases recorded in the Medical Examiner's Office was of considerable interest as roentgen treatment had been well carried out but, on operation for tonsils and adenoids, the patient had died, autopsy revealing a thymus that weighed 50 Gm. I wish that an opinion based on clinical information could be formulated that would have a value for those held responsible for the condition of a child at the time of operation, and that would relieve physicians of the criticism of neglect, so often made when the thymus was not known to be enlarged because no roentgenogram was obtained.

Head-Banging in Young Children and Its Relation to Abscess. Dr. Alfred Hand.

The head-banging discussed is that first described by Gee, seen in apparently normal and healthy young children and infants, occurring usually when they are

just put to bed and consisting of beating the head against the pillow or the sides of the crib with such violence as sometimes to cause contusions, the acts being repeated for from several minutes to several hours and recurring more or less frequently during the night.

Little attention is paid to the subject in the textbooks on children's diseases, nearly half of them omitting all reference to it, and the majority of the others making only casual mention of it in connection with a group of other so-called habits; some writers attribute it to such conditions as rickets, dentition, malnutrition, intestinal irritation, cachexia from tuberculosis or even "no provocation."

The most complete handling of the subject was given by Still ("Common Disorders and Diseases of Childhood"), who observed it to be varied sometimes with head-rolling; as the latter, in a large group of cases, seemed to bear some relation to latent disease of the middle ear, he suggested a similar relation between the banging and otitis, though not to the same degree. He pointed out that both banging and rolling precede by several weeks the development of a discharge from the ear; in those patients in whom otitis does not develop, the age period from 6 months to 5 years suggests dentition as the probable cause for the reflex irritation.

Admitting the possibility of the factors mentioned by Still, it is felt that a more constant source of irritation in this age period is the obstruction to respiration by adenoid vegetations, which is especially aggravated when the head is low, as then the secretions tend to accumulate in the nasopharynx. Thus, at first the movements of the head are purposeful and are made in an attempt to free the air-passages; in their severity, they often drive infective material into the eustachian tube with the subsequent development of otitis.

Removal of the adenoids is not without some influence for good, ranging from "slightly better" to a complete cure. Continuance of the banging may depend on the irritation of an erupting tooth, acute or chronic congestion of the nasal mucosa or some other reflex cause, with the further element of habit if the banging has been of long standing. Source of irritation should be carefully sought and removed, and the habit element treated like any other habit in children susceptible to moral suasion.

DISCUSSION

Dr. Max Schaap: I think that what Dr. Brentnemann said regarding the object of the thymus may also be said about tics. I do not know of any subject in pediatrics that is so chaotic and about which so little objective knowledge can be obtained.

In reading the literature on the subject, it seems to me that the only hope of arriving at the pathogeneses and ultimately the treatment of these common disorders is the one given by Pavlow, in other words, the philosophy of the conditioned reflex based on his physiologic technic. If one reads about the work that he has done on animals, one is impressed with the fact that he has been able to produce and reproduce functional disorders similar to tics through the changing of the equilibrium between the excitatory and the inhibitory stimuli.

With that as a basis, I have tried to see if I could apply the so-called conditioned reflex idea in the treatment for all kinds of tics.

I carefully observed a normal child, about 3 years of age, over a long period of time. I found that his biting of the lips had always been the result of a cold, a nasal infection or some other respiratory infection that has produced a chapped condition of the lips. In this instance the unfavorable irritant was the chapped condition of the lips; if it was allowed to persist, an unfavorable conditioned reflex (lip biting) would result. I prevented such a tic by curing the physical condition each time it appeared. The same reasoning can be applied to two cases of head-banging, both in infants who had resisted many forms of treatment for over six months. Every night for from three to five hours, they banged their heads and swayed their bodies.

I do not want to give the impression that what I gave was the specific therapy, but this was the process followed: The infants were treated in the hospital. We gave them each 25 grains (1.16 Gm.) of chloral hydrate for seven nights in succession, with the idea that if we could do what Pavlow suggested, we might be able to break up the unfavorable conditioned reflex that had been established. They were then allowed to be taken home and, in the second week, the dose was decreased 2 grains (0.13 Gm.) every night. We continued this treatment for three weeks. During that time, the head-banging stopped altogether during the night, as one would expect, and after that the head-banging that occurred during the day gradually stopped. Those two infants have been observed for about six months since they were first treated and they have had no recurrence to date. Along with that treatment, of course, we changed their regimen entirely, which was poor. Whether it was the chloral hydrate that broke up that unfavorable circle of association, whether it was a complete change of environment or whether it was something else, I am not prepared to say.

Dr. Charles G. Kerley: I have had an opportunity to see a number of these cases, which were practically all hangovers from early bad habits of petting and rocking. The children had been put to sleep by the old-fashioned custom of rocking in the New England rocking chair. When they became too old for this method, they were put into the crib; there they missed the swaying or rocking motion and continued it themselves. The head-banger and the head-roller belong in the same class. In order for a child to obtain any satisfaction from the banging there must be a firm surface for him to knock against. It has always seemed to me to be a vicious habit in the spasmophilis type of child. A number of years ago, a boy, 4 years of age, not only disturbed his own family but the neighbors as well by head-banging. A swaying hammock was purchased in which he was placed to sleep. He tried the head-banging but there was nothing to bang against, and he promptly stopped. Other children have since been treated in the same manner and with entire success.

Dr. Hand: I wish to thank Dr. Kerley for the suggestion of the cradle and I will investigate it in any future case. Head-banging is, of course, a habit and like all habits has some cause that must be removed before it can be dealt with successfully.

The Seasonal Incidence of Some of the Diseases of Childhood. Dr. Charles Herrman.

A summary of this paper is as follows:

1. Human beings are subject to many of the same biologic laws as plants and animals.

2. The physical, physiologic and chemical conditions of the body differ at different seasons of the year.

3. The time of greatest susceptibility to many diseases is in the late winter and spring, the period that Moro has termed the biologic spring.

4. As several functional neuroses and constitutional conditions as well as infectious diseases present this seasonal incidence, it seems unlikely that an increased virulence of infectious material is the primary etiologic factor.

5. The injurious effect seems to depend on a sudden transition, an abrupt change in some meterologic element. Apparently there are certain persons who are unable to adjust themselves quickly to these sudden changes.

6. Although it is impossible at the present time to say definitely what the exciting agent is, it is most likely some form of radiation.

7. The fact that some of the functional neuroses are much more common in some years than in others would support such a hypothesis.

8. Experimental work on laboratory animals would seem to offer the most promising field for a solution of the problem. In such experimentation the vari-

ous factors involved could be separated, modified and controlled, the effect of different forms of radiation of different wave lengths determined and artificial climates produced.

9. As the vast majority of persons cannot readily move to a different climate, and as one cannot control to any great extent the air one breathes and the radiation to which one is exposed, efforts must be directed largely to increasing the resistance of the person. This can be done mainly in three ways: by preventing the birth of the defective and unfit, thus raising the average resistance of the community; by active immunization of infants against the infectious diseases; by providing infants, children and pregnant and lactating mothers with a diet containing an adequate amount of vitamins, and by exposing them out-of-doors in the winter and spring so that they may increase their ability to rapidly adjust themselves to sudden changes in climate.

10. The solution of these problems will require the combined efforts of biologists, physicists and physicians.

DR. F. F. TISDALL: Two or three years ago we studied about 5,000 records in Toronto on the age, sex and seasonal incidence of certain diseases, and it is remarkable how closely these figures correspond to the figures given by Dr. Herrman, as far as scarlet fever and measles are concerned.

Our figures on intussusception and pyloric stenosis, however, were different from those of Dr. Herrman. In his charts he showed that pyloric stenosis occurred more frequently in the winter months. From the records of 150 cases we found that it occurred more frequently in the summer months. We found that many of the other diseases, such as scarlet fever and measles, have their height in the spring, while whooping cough, in contradistinction, has its height in the summer months. This makes one suspect that a child who has a cough in the summer time has whooping cough.

In the vast majority of diseases that we studied, 60 per cent of the cases occurred in males. In the reports of many diseases, the authors comment on the fact that males are attacked more frequently than females. That seems to be the usual course of events in the vast majority of diseases. We found that poliomyelitis and tetany have the most marked seasonal incidence.

DR. HERRMAN: Dr. Tisdall's point that the majority of cases of pyloric stenosis occur in males is interesting.

In experimental work on animals by Brodie and Moore it was shown that by withholding vitamin B it was possible to produce pyloric stenosis, and that the disease occurred more frequently in males than in females.

It is extremely interesting to note that whooping cough is the only communicable disease of childhood that shows a greater morbidity and mortality in females than in males. So far as I know, no one has explained that fact.

(To be continued)

PHILADELPHIA PEDIATRIC SOCIETY

Stated Meeting, March 11, 1930

RALPH M. TYSON, M.D., *President, in the Chair*

THE RELATIONSHIP OF DEFICIENCIES IN VITAMIN A AND D TO INFECTION. Presented by DR. WILLIAM BRADFORD, Rochester, N. Y.

A review of the clinical and experimental work bearing on the subject was given. The purpose of the paper was to report the results obtained with artificially infected rats that were suffering from deficiencies of vitamins A and D. The

organism used was a bacillus of the *mucosus-capsulatus* group, previously isolated from suppurative lesions of rats deficient in vitamin A. Attempts to infect by way of the upper respiratory tract were not successful. The dose for intraperitoneal inoculation was previously determined by the injection of a group of stock rats of the approximate weight of those to be infected. The doses usually ranged between 0.25 and 0.04 cc. of a 1:10 dilution of a twenty-four hour broth culture. The dose used was that amount which just permitted a normal rat to live.

A group of twenty-three rats was fed on a diet deprived of its vitamin A content. The controls (twenty-three animals) received the same diet plus daily doses of a tested brand of cod liver oil. As the development of A deficiency progressed in the rats, subgroups were infected at the end of four, six, eight and ten weeks, respectively. The mortality, the length of survival after infection and the anatomic observations were carefully recorded.

In the group deficient in vitamin D, there were twenty-three test animals and twenty-three controls. All were fed the Steenbock ricket-producing diet. The controls received vitamin D in the form of daily doses of viosterol. Subgroups were infected at the end of intervals of four, six and eight weeks.

In the group deficient in vitamin A one animal survived and twenty-two died. Six of the controls lived and seventeen died. The average duration of life after infection was ten hours in the test group, while it was thirty-one hours in the control group. Subgroups showed increased susceptibility to the infection before there was clinical or anatomic evidence of deficiency in vitamin A.

In the group deficient in vitamin D, the results in the test and in the control groups were similar. Seven of the rachitic rats survived the infection and sixteen died. The average duration of survival was nineteen hours—almost twice as long as in the animals deficient in vitamin A. Of the controls, seven lived and sixteen died. The average duration of survival in the control animals was twenty-one hours after infection.

The study suggests that deficiency in vitamin D per se, is not so important as a factor in lowering resistance to infection as is generally supposed. While animals with florid rickets readily succumb to infection, those suffering in mild or moderate degrees do not. The importance of inoculating the animals at intervals throughout the course of the deficiency-development instead of at the terminal stage is pointed out. From the clinical point of view, it is suggested that a diet so low in vitamin D as to lead to markedly active rickets is probably also relatively low in vitamin A, and this fact may explain why some rachitic children suffer from infections.

NUTRITION AND INFECTION IN INFANCY. Presented by DR. SAMUEL W. CLAUSEN, Rochester, N. Y.

Relative resistance to respiratory infections depends among other things on good nutrition. A review of the literature dealing with animal experimentation and with clinical observations indicates that among the most important dietary factors that contribute to increase resistance are the vitamins. Whereas vitamins D and C appear to be of minor importance in this regard, it is evident that deficiency of vitamin B may lead to intestinal infections, and that marked deficiency of vitamin A leads especially to spontaneous respiratory infections. Relative deficiency of vitamin A in animals may also lower resistance to experimentally induced infections.

The possible effect of relative deficiency in human beings was studied in a series of hospital patients. Evidence was obtained in mild and severe respiratory infections that the administration of cod liver oil, per se, was without effect. The presence or absence of rickets when considered alone was without effect. On the other hand, good nutrition as a whole was found to be definitely associated with fewer severe respiratory infections. In the group of well nourished infants, severe infection was found to be associated with exposure to infection in the

family, whereas this was not a prominent factor in the badly nourished group. Dr. Clausen's observations clearly illustrated the operation of two important factors in the causation of respiratory infections: (1) the presence of virulent microorganisms and (2) the lowering of nonspecific resistance by faulty nutrition. It is not possible to regard faulty nutrition as due to one factor alone, such as the low intake of vitamin A, but it must rather be regarded as a complex of many factors.

DISCUSSION

DR. LUCE CLAUSEN: I was asked especially to open the discussion of the subject of the relationship of light to deficiency in vitamin A. In this connection, the work of Coward is of interest. Coward found that light from a mercury vapor quartz lamp caused an acceleration of the formation of vitamin A in living plant tissue, but that it did not influence the ultimate amounts of the vitamin contained in the tissues. Temperature was also a factor, as she found the amount of vitamin A in etiolated wheat shoots to be an inverse function of the temperature at which they were grown.

With regard to the effect of light on animals suffering from a deficiency of vitamin A, Dr. Bradford and I undertook experiments to investigate this. We exposed rats deficient in vitamin A to bands of isolated radiations transmitted from a carbon arc lamp. Our results as to the value of any of the radiations used were entirely negative. All the animals in our experiments showed the widespread infective lesions characteristic of deficiency in vitamin A. From the purely scientific standpoint, there is little evidence for the use of radiation therapy as a protective measure against infection. I know this is a controversial subject, and I think it would be nice to get the opinion as to its value from clinicians here who have had experience in the use of radiation therapy.

DR. PERCIVAL NICHOLSON: The society greatly appreciates this interesting piece of work that has been submitted by Dr. Bradford and Dr. Clausen. I cannot say much concerning the deficiency of vitamin A from a laboratory standpoint. Some interesting work has been done by Edenough and Hill in relation to resistance to infection by radiation with ultraviolet light. Edenough took rabbits, shaved them carefully and tested the bactericidal power of the blood before and after radiation. He found that when he radiated small areas with a rather low intensity, there was a marked increase in the bactericidal power of the blood; when he increased these areas, the power was diminished. In his original work he used erythema doses, but he has found that he does not need to use an erythema dose and that less than a dose has greatly increased the bactericidal power of the blood. Some of the earlier work in regard to lowering infection, done in New York with control cases, seemed to give entirely negative results, as the experiments in radiation were done illogically as to dosage and probably a great overdose was given in some cases. Since then, the dosage has been lowered. Now it is found that in almost all of these cases radiation is used too often and at too close distances. I have had considerable experience with children with low resistance to infection, and have found that there was a marked increase during the winter months. I have followed the progress of four or five very much undernourished children who were treated by irradiation for two or three winters. They increased in weight so much that their teachers remarked on the changes in mental as well as in physical growth. I was much interested in the results of Dr. Clausen in a family in which there were several patients. One interesting factor is that children who have good nutrition, have a good resistance. It requires a severe infection to break that resistance, and as a result of not developing a low grade infection, they do not produce antibodies. These children, when once their resistance is broken, have severe infections. In other words, many children who have a little lower resistance may have infections and develop a low grade immunity which other children not having such infections do not develop. A great many factors come into this picture. It is exceedingly difficult to draw conclusions from hospital records. It has been interesting to me to see the way these diagrams have demonstrated certain facts and I hope they will work out successfully. I have no doubt some of these points will.

DR. JOHN P. SCOTT: I should like to ask Dr. Clausen if he explains the secondary influx of infections in the months of September and October on the basis of diseases of allergy or on the basis of an A or D deficiency?

DR. A. M. DANNENBERG: I had the impression that Dr. Dean of St. Louis reported at a recent meeting in Philadelphia that rabbits fed on a diet containing vitamin A and infected with some nasorespiratory type of infection had survived and those that had been infected and deprived of vitamin A, consistently died. I should like to ask if Dr. Bradford has knowledge of that work.

DR. WILLIAM BRADFORD: In regard to the question about Dr. Dean's report, I think he was citing the work of Dr. Amy Daniels. Dr. Daniels and Dr. Armstrong were among the first to show that when rats were fed on diets deficient in vitamin A, these lesions could be demonstrated. They occurred quite consistently in the nasopharynx and middle ear. Abscesses of the tongue and abscesses of the urinary tract and of the lungs were also noted. Rats given an adequate supply of vitamin A failed to show these spontaneous reactions. This observation has led such workers as Mellanby and others to call vitamin A the antiinfective vitamin. I believe that there is not yet enough evidence to say that, however.

DR. SAMUEL W. CLAUSEN: I would like to say a word about Dr. Nicholson's discussion. The question with which I was concerned was more particularly the D factor and the relationship of radiation to that. I think that probably there is a nonspecific effect of radiation which has nothing to do with vitamin D. One wonders whether that is an effect of light per se or whether it is entirely nonspecific, and might also be brought about by applying to the skin any other irritating agent. For example, Leonard Hill and other workers using rabbits showed that when mustard plasters or mustard water is applied to the skin they could demonstrate leukocytosis and increased bactericidal power of the blood and that when the skin was too strongly stimulated this action disappeared. That raises the question as to whether this effect of light may not be due to nonspecific activity. I think that there is no question that often too large doses of radiation are used in the treatment for rickets. I quite agree with Dr. Nicholson about statistical records. It is difficult to draw conclusions from them. I think, however, that one can make use of such a study to discover problems for further investigation. I have not been able to satisfy myself about Dr. Scott's question regarding the appearance of infection in September and October. I do not believe it is due to allergy, because it affects the youngest children and not particularly the older ones. I think that it may have something to do with the rather sudden changes of temperature that occur at that time of the year. It may have something to do with the return of the older children in the family to school.

Book Reviews

Tuberculosis Among Children. By J. Arthur Myers, Ph.D., M.D., F.A.C.P. With Chapters by C. A. Stewart, M.D., Ph.D., and Paul W. Giessler, M.D. Introduction by Allen K. Krouse, M.D. Price, $3.50. Pp. 208, with illustrations and a colored plate. Springfield, Ill., Charles C. Thomas, 1930.

"In the period of infancy and childhood lies the fountain head of tuberculosis" (preface). Not all cases of tuberculous disease in adult life originate during these early age periods, but the fact that tuberculosis in childhood had prepared the way and left its mark in more than 50 per cent of clinical cases in young adults is a striking observation. Fortunately, during infancy and childhood tuberculous infection quickly registers its presence, and at this time the study of the development and progress of the disease is most productive of practical results. The author's service as physician-in-chief of the first special hospital for tuberculous children in the United States has provided him with much of the valuable material which he has incorporated in this small but comprehensive monograph of 208 pages. It is an eminently practical manual, and should prove of the greatest value to pediatricians, school physicians and, especially, physicians engaged in family practice. The various diagnostic measures are fully and clearly described, especially those most valuable in childhood, viz., tuberculin skin tests and roentgen examination. The newer ideas concerning allergy and immunity in relation to tuberculosis are discussed, and the results of the latest clinical investigations are summarized. On every page the author has sought to correlate modern ideas concerning the etiology, pathogenesis and diagnosis of the disease with the ultimate problem of prevention. The manifestations of tuberculous infection and disease in infancy, childhood and the teen ages are well covered, including special chapters by C. A. Stewart and Paul W. Giessler on "Tuberculous Meningitis," "Tuberculosis of Bones and Joints" and "Chronic Non-Tuberculous Basal Pulmonary Disease in Childhood." An especially valuable chapter on "Some Dangers to Children from Tuberculosis Among Elderly People" rounds out the book. Each chapter is followed by an excellent summary, and by a sufficiently comprehensive, carefully chosen and up-to-the-minute bibliography.

Die Ohrenleiden der Kinder. By Dr. Max Meyer. Price, 12 marks. Pp. 166, with 41 illustrations, some colored. Berlin: S. Karger, 1930.

This book constitutes volume 26 of "Abhandlungen aus der Kinderheilkunde und ihren Grenzgebieten." It is in the form of twelve lectures to which are appended a list of prescriptions designed for use by the general practitioner. Beginning with the description of the instruments used for otoscopic examination, the anatomy, function of the ear, functional testing of hearing and diseases of the external ear are discussed. Then follow descriptions of catarrhal diseases of the middle ear, otosclerosis and chronic otitis media. Tuberculosis and syphilis of the ear together with lateral sinus thrombosis and intracranial complications are discussed. In conclusion, traumatisms of the ear are considered. In the development of many aural conditions in the child as contrasted with the adult, there are certain variations due to the difference in the anatomy of the mastoid process, the external auditory canal and the eustachian tube of a child as compared with those of an older person. The author endeavors to point out to the general practitioner these peculiarities and their clinical bearing.

The book emphasizes from a practical standpoint the methods of examination to be employed and the significance to be attached to the various symptoms connected with the ear in childhood. The author uses simple terms, which are very

clear, should be easily understood and cannot fail to give the proper information to the pediatrician. Attention is called to the need of great care in the handling of the tissues, and the avoidance of all measures which might be injurious to the child, the fact being emphasized that all difficult manipulations and certainly all operative work should be referred to the otologist.

The author insists on the careful examination of the child in order that serious symptoms be promptly recognized and treatment carried on by the specialist to whom the case may be referred.

Although a more elaborate work on the subject has previously been published, this compact, well written book by Meyer fills an important niche, and should prove of inestimable value not only to practitioners and pediatricians, who are in the habit of examining the ears of their patients, and carrying out many of the simpler measures such as the removal of cerumen, but to otologists, who will be impressed with the importance of many aspects of the otologic troubles of the young child.

PUBLICATIONS FROM THE ROBERT DAWSON EVANS MEMORIAL FOR CLINICAL RESEARCH. 1. ENDOCRINE STUDIES. Pp. 220. Boston: Massachusetts Memorial Hospital, 1929.

This book consists of seven collected papers on studies of the endocrine glands. These include clinical and experimental studies on the methods for the diagnosis of abnormal functions of the pituitary gland, the thyroid and the male and female gonads and pluriglandular syndromes. The last two papers are devoted to cases simulating glandular disorders, and their differential diagnosis.

Directory of Pediatric Societies

NATIONAL

American Medical Association, Scientific Assembly, Section on Diseases of Children

Chairman: Dr. C. A. Aldrich, 545 Lincoln Ave., Winnetka, Ill.
Secretary: Dr. Alfred A. Walker, Highland Plaza Apartments, Birmingham, Ala.
Place: Philadelphia. Time: 1931.

American Academy of Pediatrics

President: Dr. I. A. Abt, 104 S. Michigan Ave., Chicago.
Secretary: Dr. C. G. Grulee, 310 S. Michigan Ave., Chicago.

American Child Health Association

President: Hon. Herbert Hoover, 370 7th Ave., New York.
Secretary: Dr. Philip Van Ingen, 370 7th Ave., New York.

American Pediatric Society

President: Dr. Philip Van Ingen, 125 E. 71st St., New York.
Secretary-Treasurer: Dr. Howard Childs Carpenter, 1805 Spruce St., Philadelphia.
Place: New York.

Association of American Teachers of the Diseases of Children

President: Jacob V. Greenebaum, 19 W. 8th St., Cincinnati.
Secretary: Dr. Ralph M. Tyson, 334 S. 21st St., Philadelphia.
Place: Philadelphia. Time: 1931.

Children's Hospital Association of America

President: Dr. Howard Childs Carpenter, 1805 Spruce St., Philadelphia.
Secretary-Treasurer: Miss Bena M. Henderson, Milwaukee Children's Hospital, Milwaukee.
Place: New Orleans, La. Time: October, 1930.

Canadian Society for the Study of Diseases of Children

President: Dr. E. A. Morgan, 160 Bloor St., Toronto, Ont.
Secretary-Treasurer: Dr. George E. Smith, 244 Bloor St., W., Toronto, Ont.

SECTIONAL

Central States Pediatric Society

President: Dr. Edward Clay Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary: Dr. A. H. Parmelee, 310 S. Michigan Blvd., Chicago.
Place: Memphis, Tenn. Time: Fall, 1930.

Southern Medical Association, Section on Pediatrics

Chairman: Dr. H. Leslie Moore, 1717 Pacific Ave., Dallas, Texas.
Secretary: Dr. Ludo von Meysenbug, 3501 Prytania St., New Orleans, La.
Place: Louisville, Ky.: November, 1930.

STATE

Alabama Pediatric Society

President: Dr. Hughes Kennedy, Jr., Highland Plaza Apts., Birmingham.
Secretary-Treasurer: Dr. John W. Simpson, 1117 S. 22nd St., Birmingham.

Georgia Pediatric Society

President: Dr. W. N. Adkins, Medical Arts Bldg., Atlanta.
Secretary-Treasurer: Dr. E. N. Gleaton, 212 E. Gaston St., Savannah.

Louisiana State Pediatric Society

President: Dr. R. A. Strong, 1551 Canal St., New Orleans.
Secretary-Treasurer: Dr. Suzanne Schaeffer, Chailie Bldg., New Orleans.

Oklahoma State Pediatric Society

President: Dr. Carroll M. Pounders, 210 W. 10th St., Oklahoma City.
Secretary: Dr. C. E. Bradey, Medical Arts Bldg., Tulsa.
Place: Oklahoma City. Time: May, 1931.

South Carolina Pediatric Society

President: Dr. M. W. Beach, 126 Meeting St., Charleston.
Secretary-Treasurer: Dr. Julian P. Price, The McLeod Infirmary, Florence.

Texas Pediatric Society

President: Dr. L. O. Dalley, 600 W. 10th St., Fort Worth.
Secretary-Treasurer: Dr. John G. Young, 3930 McKinney Ave., Dallas.

Virginia Pediatric Society

President: Dr. Franklin D. Wilson, 136 York St., Norfolk.
Secretary: Dr. J. B. Stone, 2042 Park Ave., Richmond.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. John Toomey, Cleveland City Hospital, Cleveland.
Secretary: Dr. A. B. Grossman, 7016 Euclid Ave., Cleveland.
Place: 2009 Adelbert Road. Time: Four meetings, from September to May.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. Gladys Boyd, 56 DeLisle St., Toronto.
Secretary: Dr. Lawrence Murray, 1870 Bloor St., West, Toronto.
Time: November 17, December 15, February 16 and March 15.

Bronx Pediatric Society

President: Dr. David I. Frey, 2065 Grand Concourse, New York.
Secretary: Dr. H. M. Eisenoff, 1018 E. 163rd St., New York.
Place: Concourse Plaza, 161st St. and Grand Concourse. Time: Second Wednesday of each month, except June, July, August and September.

Brooklyn Pediatric Society

President: Dr. Joseph F. Paulonis, 1357 Bushwick Ave., Brooklyn.
Secretary: Dr. Irwin Schiff, 658 Eastern Parkway, Brooklyn.
Place: Kings County Medical Society Bldg. Time: Last Wednesday of each month, except June, July and August.

Central New York Pediatric Club

President: Dr. Frank Vander Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Fourth Thursday of October, January and April.

Chicago Pediatric Society

President: Dr. Arthur H. Parmelee, 310 S. Michigan Blvd., Chicago.
Secretary: Dr. Bert I. Beverly, 8 S. Michigan Ave., Chicago.
Place: City Club. Time: Third Tuesday of each month.

Detroit Pediatric Society

President: Dr. Wyman C. C. Cole, 2970 W. Grand Blvd., Detroit.
Secretary: Dr. Charles A. Wilson, 71 E. Perry St., Detroit.
Place: Children's Hospital of Michigan. Time: No fixed date; approximately once a month.

Fulton County Medical Society, Pediatric Section (Atlanta, Ga.)

Chairman: Dr. Lee Bivings, Exchange Bldg., Atlanta.
Secretary: Dr. William Kiser, Medical Arts Bldg., Atlanta.
Place: Academy of Medicine, 32 Howard St. Time: Second Thursday of each month from October to April, 8 p. m.

Memphis Pediatric Society

President: Dr. G. J. Levy, 899 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. W. R. Graves, 1024 Madison Ave., Memphis, Tenn.
Place: Memphis General Hospital. Time: Second Tuesday of each month.

Milwaukee Pediatric Society

President: Dr. M. G. Peterman, 167 17th St., Milwaukee.
Secretary: Dr. F. R. Janney, 418 E. North Ave., Milwaukee.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

Nebraska Pediatric Society

President: Dr. H. B. Hamilton, 434 Aquila Court Bldg., Omaha.
Secretary: Dr. George L. Clark, 1817 Vinton St., Omaha.
Place: As announced by committee. Time: Second Thursday of each month from October to June, inclusive, 6 p. m.

New England Pediatric Society

President: Dr. Grover F. Powers, New Haven, Conn.
Secretary: Dr. Gerald Hoeffel, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: October, January and March.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Hugh Chaplin, 39 E. 75th St., New York.
Secretary: Dr. John P. Caffey, Babies' Hospital, 167th Street and Broadway, New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

North Pacific Pediatric Society

President: Dr. W. F. Patrick, Medical Arts Bldg., Portland, Ore.
Secretary: Dr. L. Howard Smith, Medical Arts Bldg., Portland, Ore.

Northern California Pediatric Society

President: Dr. Edward B. Shaw, 384 Post St., San Francisco.
Secretary-Treasurer: Dr. Lloyd Hardgrave, 384 Post St., San Francisco.
Place: Various teaching schools. Time: Monthly.

Northwestern Pediatric Society

President: Dr. E. S. Platou, 730 La Salle Bldg., Minneapolis.
Secretary: Dr. F. G. Hedenstrom, 218 Lowry Bldg., St. Paul.
Place: University Campus and Rochester, Minn. Time: Winter, Spring, Summer, Fall.

Philadelphia Pediatric Society

President: Dr. Ralph M. Tyson, 334 S. 21st St., Philadelphia.
Secretary: Dr. John D. Donnelly, 115 Bryn Mawr Ave., Bala-Cynwyd, Pa.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to June, inclusive.

Pittsburgh Pediatric Society

President: Dr. David H. Boyd, 200, 9th St., Pittsburgh.
Secretary: Dr. Theodore O. Elterich, Highland Bldg., Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate months from October to April, inclusive.

Richmond Pediatric Society

President: Dr. Basil B. Jones, 2618 Grove Ave., Richmond, Va.
Secretary-Treasurer: Dr. John S. Weitzel, 3103 W. Franklin St., Richmond, Va.
Place: Westmoreland Club, 601 E. Grace St. Time: First Thursday of each month (other than during the summer).

Rochester Pediatric Society

President: Dr. John Aikman, 184 Alexander St., Rochester, N. Y.
Secretary: Dr. Howard F. Rowley, 176 S. Goodman St., Rochester, N. Y.
Place: Arranged by program committee. Time: First Friday of each month from October to May.

Rocky Mountain Pediatric Society

President: Dr. Bernard C. Dorset, 1612 Tremont St., Denver.
Secretary-Treasurer: Dr. Wilford W. Barber, 227, 16th St., Denver.
Place: Children's Hospital, Denver. Time: Third Saturday of each month from September to May, inclusive, 2:30 p. m.

St. Louis Pediatric Society

President: Dr. Gustave Lippmann, 3720 Washington Blvd., St. Louis.
Secretary-Treasurer: Dr. Katherine Bain, 3720 Washington Blvd., St. Louis.
Place: St. Louis Children's Hospital. Time: At least once a year and contingent thereafter on the arrangement of a suitable program.

Seattle Pediatric Society

President: Dr. Vernon W. Spickard, Cobb Bldg., Seattle.
Secretary: Dr. Raymond H. Somers, Cobb Bldg., Seattle.
Place: College Club. Time: Third Friday of each month, 7 p. m.

Southwestern Pediatric Society

President: Dr. William S. Bowers, 1136 W. 6th St., Los Angeles.
Secretary: Dr. Fred L. Glascock, 1136 W. 6th St., Los Angeles.
Place: University Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. W. D. Lyon, 101 S. Balch St., Akron, Ohio.
Secretary: Dr. John P. Parsons, 320 S. Division St., Ann Arbor, Mich.
Place: Ann Arbor, Mich. Time: November 14 and 15, 1930.